A COMPARISON OF MEDICAL AND PHYSICAL THERAPIES IN THE MANAGEMENT OF FACIAL ARTHROMYALGIA (TEMPOROMANDIBULAR JOINT DYSFUNCTION)

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Declaration:

I, Rachel M A Leeson, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

This thesis reports on a randomised controlled trial of medical and physical therapy in the management of chronic temporomandibular joint pain and dysfunction.

The literature review first explores the meaning and measurement of chronic pain. The anatomy and dynamic function of the temporomandibular joint and associated musculature is then introduced before describing the pain and dysfunction which affects this specific region. The development of terminology, classification and epidemiology is addressed to provide a basis for understanding the condition. A discussion of the presumed multifactorial aetiology and current management follows, with focus on the two areas of specific interest in this study the physical and medical therapies

The study methods, results and discussion are presented in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

A referral cohort of 1,038 subjects were screened and assessed. 250 subjects met inclusion criteria and agreed to participate with informed consent. Subjects were randomised into four groups: medical therapy, placebo, occlusal bite guard, medical therapy and occlusal bite guard. A three month treatment phase and a six month follow-up phase were then conducted.

The first section of the results examines the referral cohort. Demographic, clinical diagnostic, and psychosocial profile are reported with treatment uptake for the trial.

The second section examines the three month trial phase, treatment efficacy and outcome. The analysis of subgroups is explored, including the characteristics of responders and non-responders to therapy in addition to outcome measures in subjects with initially high pain scores and high levels of depression. The final section analyses reasons for patient withdrawal and non compliance before examining the follow up phase post therapy for maintenance of improvement.

Both primary and secondary outcome measures revealed significant improvement in pain amongst all four groups which was maintained during the follow-up phase.

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ABBREVIATIONS

Therapeutic groups: synonyms used in the thesis

Group 1 = Active medical therapy, fluoxetine,(Prozac) 20-40mg.

Group 2 = Placebo medical therapy

Group 3 = Physical therapy, stabilization appliance, splint, bite guard, occlusal appliance

Group 4 = Combined therapy, fluoxetine, (Prozac) medication and splint

AOB	Anterior open bite
ARR	Absolute relative risk
BDI	Beck Depression Index
BNF	British National Formulary
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EBM	Evidence based medicine
ICP	Intercuspal position
ITT	Intention to treat
Kellner	Kellner Illness Attitude Scale
MPI	Multidimensional Pain Inventory
MPQ	McGill Pain Questionnaire
MRI	Magnetic resonance imaging
NNT	Numbers needed to treat
ns	Not significant
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthrosis
OB	Over bite
OJ	Over jet
OR	Odds ratio
OVD	Occlusal vertical dimension
p	p-value
PDA	Personal Digital Assistant
RCP	Retruded contact position
RCT	Randomised controlled trial
RDC	Research Diagnostic Criteria
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TMD	Temporomandibular disorders
TMJ	Temporomandibular joint
TMJD	Temporomandibular joint dysfunction
VAS	Visual analogue scale
WHO	World Health Organization
WMA	World Medical Association
>25%	Greater than 25%
>50%	Greater than 50%

INTRODUCTION

CHAPTER I

PAIN

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1.0 THE MEANING OF PAIN

1.1 Definitions of pain

Why do people suffer pain? Over the centuries, philosophers, theologians and physicians have struggled with this enigma. Even in the 21st century our understanding, although more enlightened, remains limited. 'Pain' originates from the Greek word 'poena' meaning a fine or penalty, which in Greek mythology, refers to a form of punishment on mankind. Everyone fears 'poena' yet no one escapes the universal but individual experience of 'pain,' an integral aspect of life. For instance, it is acknowledged that without transient pain as an early warning system we eventually die due to tissue damage and uncontrolled infection as seen in congenital analgesia, a rare neurological condition where pain is not felt (Wall 1999). However, suffering and prolonged pain serves no useful purpose and it is this phenomenon, which is the most complex to unravel.

The Oxford English dictionary ,2005, defines pain as suffering of body or mind. This identifies the two components involved in pain the physical or sensory body and the emotional or psychological mind. Both elements, rather than separate, are considered extricably intertwined, each element contributing to a lesser or greater degree in various pain conditions. This leads us to the currently most acceptable definition of pain as defined by the International Association for the Study of Pain. "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage "(Merskey and Bogduk,1996). In order to appreciate the derivation of this definition it is first necessary to understand the progression of pain theory from the mechanistic, specificity theory to the current biopsychosocial model of pain.

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1.2 Theories of Pain

Epicurus (340-270B.C.) proposed injury to equate directly to pain (Everson 1991). This philosophy of linear causation was influential in the development of pain theory and the mechanistic model of pain, dominant in western medicine until the mid 1960's (Horn and Munafo, 1997)

1.2.1 Specificity theory

The mechanistic approach to pain was exemplified by Descartes who in1664 published a theory of pain transmission, which became known as the specificity theory (Melzack and Wall 1996). It was proposed that independent of other somatic sensation pain was conveyed from sensory apparatus by threads along a pathway from peripheral site to a central location in the brain.The receptors and specific pathways to the spinal cord and brain required investigation. Von Frey (1894) developed the theory by suggesting that free nerve endings numerously distributed on the skin surface were the specific peripheral pain receptors. Unique types of pain fibre were later discovered A-delta (Aδ) C and A-beta (Aβ) of varying diameter and myelination. Transmission, velocity and quality of pain experience varied between fibres, each proposed to have a specific pathway to a distinct area in the brain, (Melzack & Wall 1996). Keele (1957) discovered the spino-thalamic tract of the spinal cord a 'pain pathway' essential for pain transmission to the brain.

The exact locations in the brain stem and thalamus of the nuclei, which receive and process pain information, continues to be unraveled (Melzack and Wall,1996, Horn and Munafo, 1997). The contribution of the specificity theory has been invaluable in the discovery of peripheral sensory fibre specificity and the pain pathway. An assumption of a

direct relationship between 'pain receptor' stimulation and the sensation of pain is however inadequate.Cartesian dualism separates mind and body, (Bonica,2001). Applied to pain this infers a sensory process with no modulation between stimulus and response and a disregard for any psychological factors. However, psychological studies confirm that pain perception and intensity of stimulus are not directly related. (Beecher, 1956, Melzack, Wall and Ty 1982).

1.2.2 Summation theory of pain

Goldsheider (1894) proposed a summation or pattern theory. Stimulus intensity and summation in the dorsal horn were considered critical determinants of pain production, (Melzack & Wall 1996). This theory acknowledged that any non-specific receptor, repeatedly stimulated, may produce pain with summation delayed or enhanced by pathology. This displaced the concept of there being only a specific type of pain receptor. Livingstone 1943, shifted the focus of attention to central summation. A reverberating circuit in the grey matter of the spinal cord initiated by normal sensory input leads to abnormal central activity with interpretation of stimuli as painful,(Melzack and Wall,1996). Although this explains the importance of the central nervous system in phantom limb pain and causalgia it does not account for the inability of spinal cord lesions to abolish phantom limb pain or pain experienced in para or quadriplegics.The short falls of specificity and summation theories to accommodate several anomalies of the pain experience, including a more active role for the brain, needed to be further addressed.

1.2.3 Gate Control theory

Melzack and Wall 1965, proposed the gate -control theory combining strengths of previous theories with new concepts. The most novel feature was 'the gate', a neural mechanism in the dorsal horn of the spinal cord, which integrates ascending afferent signals from the peripheral nerves and modulates descending efferent signals from the brain and central nervous system (Melzack with Wall, 1996).

This was a modulatory rather than a direct transmission theory (Horn and Munafo 1997)

Ascending signals from Aβ, Aδ and C fibres were known to terminate in the dorsal horn.

The balance in activity between these large and small diameter fibers effectively "opened and closed" the gate facilitating or inhibiting neural transmission of pain. Aβ, large diameter fibers, exhibiting an inhibiting effect on the relay of nerve impulses whilst preponderance of the slower conducting, small diameter Aδ and C fibers increased pain transmission.

The cells comprising the substantia gelatinosa, in the dorsal horn, seemed to be responsible for modulating input from the afferent fibers to spinal cord transmission (T) cells, which then convey impulses to ascending spinal cord pathways (Wall 1964). It was proposed that gating mechanism influenced by the Central control Trigger is a further system of large diameter fast conducting fibers, which activate selective cognitive processes.

The descending neuronal impulses were also proposed to influence the gate, considered predominantly inhibiting, (Melzack and Wall 1996)

A central system was proposed relating to pain behavior and experience activated when T cell output exceeds critical level. These sites in the reticular and limbic systems of the

brain correspond to cortical projection pathways for pain. In addition, it was believed influence on the gating mechanism could be linked to a range of factors unrelated to specific sensory pain transmission such as cognitive influences, attention, meaning, anxiety, past experience and memory of pain. The mechanisms producing these effects were unclear when published yet a vital concept in explaining inter and intra individual variation in response to an identical injury.There was also finally an acknowledgement of the active role of the human brain in analyzing and influencing the perceptual and sensory world of pain. Although the gate remains a theoretical construct the existence of the neural mechanism in the dorsal horn is no longer disputed (Larbig 1991)The ability to integrate: psychological, behavioural and physiological components of pain into the one model created a more holistic approach and a paradigm shift in the understanding of pain (Grahek, 1991)

1.2.4 Beyond the gate and neural plasticity

The gate control theory presented pain as a dynamic process but long term changes in central nervous system or the extent of prolonged gate opening with sensitization to pain were not yet taken into account. (Loeser & Melzack 1999).

Altered function or hypersensitivity of the central nervous system following peripheral injury was suggested by Stuge in the 1880's and a decade later by MacKenzie 1893 who considered the spinal cord the site of hypersensitivity (Coderre et al. 1993).Transient changes in the dorsal horn neuron sensitivity to further stimulation by noxious peripheral stimuli was found in the late 1970's but sustained changes in central excitability was demonstrated in animal studies by Woolf et al. 1983. Peripheral sensitization and increase in spinal cord excitability following noxious stimulation were maintained even after local

anaesthetic at the site of injury, where 10 times the dosage of morphine was required to reverse excitability as to prevent establishment (Woolf and Wall 1986)

Peripheral damage was also shown to lead to expansion of the nociceptive fields of spinal neurons resulting in pain following stimulation at a site other than the original injury. Nociceptor function is known to be influenced temporarily by the inflammatory mediators surrounding the tissue injury during body healing (Loeser and Melzack, 1999). However, massive nociceptive input, due to excitatory toxic effects of amino acids can permanently change spinal cord function resulting in chronic long term pain following an acute injury (Dubner and Rude 1992;Doubell,Mannion and Woolf,1999).

Increased excitability in neurons in the spinal and medullary dorsal horn caused spontaneous neuronal activity, lowered pain thresholds and hyperalgesia (Dubner and Rude 1992) Pain transmission leading to central changes were demonstrated where repeated activation of C fibers resulted in an augmented response to subsequent C fibre input, termed the "wind up" phenomenon (Dikenson, 1991). Changes at both spinal and peripheral sites were suggested with interaction between excitatory amino acids, opioids, monoamines and non opioid peptides which may persist for days following injury. Scholz and Woolf, 2006, in an updated gate control theory, suggests altered gene expression in the dorsal root ganglion may be responsible for the persistent pathological process of pain arising from increased excitiation and decreased inhibition within the spinal cord.

Opioid mechanisms themselves also exhibit plasticity but to what extent changes are related to behavioural and psychological functioning is unknown (Lipman et al. 1990).

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"Central sensitization " with activation of multiple cortical and sub cortical regions may be partly responsible for failure to provide substantial chronic pain relief from both surgical and medical interventions, (Price, Mao and Mayer 1997)

Clinical pain states such as phantom limb pain or pain below the level of spinal cord transection indicate the brain appears capable of generating pain in the absence of peripheral nociceptor or spinal cord input. A pattern- generating mechanism, or neuromatrix is hence thought to exist into which input data converge on an image of the body (Codere, 1993; Melzack, 1990). Perception of pain is generated by output from this neuromatrix regulated by sensory, affective and cognitive activity. Expectation and environmental cues may generate or perpetuate previously conditioned nerve impulse patterns producing somatic sensation. In contrast, modulation may diminish or prevent the perception of a normally noxious event.

1.3 Identification of pain

1.3.1 Nociception and perception

Nociception is derived from the Greek word "nox" meaning harm or damage and is the detection of noxious stimuli. A dual stage process, it involves transduction of a noxious stimulus by peripheral nerve endings, influenced by inflammation or neural change in their immediate environment followed by transmission of these signals to the central nervous system. Nociception is not synonymous with the subjective state of pain but activation of nociceptive pathways is usually the origin of the pain. However, nociceptive input can be modulated at every level of the afferent pathway from peripheral nerve to cerebral cortex.

Restoration of transducer activity to the resting state by local anti inflammatories, local or regional anaesthesia or more sophisticated downstream modulation can all prevent nociception attaining the status of pain. If nociception results in pain, the experience of perception and tolerance are profoundly influenced by the context in which the event occurs notably the individual's affective state, levels of distress, health, immunological status and previous pain experience.

The perception of pain can occur not only from the noxious stimulus of peripheral injury or disease but also from lesions of the central nervous system or without any observable cause. When a diagnosis for pain is identifiable, the cause where appropriate can be eliminated and appropriate treatment provided. However, diagnosis often gives limited indication of suffering or impact on life since physical findings do not correlate to the degree of observed pathology (Turk and Melzack, 1992). Distinct emotional and distress components also require evaluation since maintenance of pain may involve a complex interaction of psychosocial factors (Melzack and Wall, 1996).

Categorizing the type of pain in descriptive terms and duration; transient, acute or chronic; are however useful in aiding diagnosis and treatment approach.

1.3.2. Acute and chronic pain

Classically, a temporal distinction is made between a short acting episode of acute pain and longstanding constant or recurrent chronic pain.

The time period, which signifies a chronic condition, is arbitrary but usually ranges from a month to six months. Bonica (2001), describes pain persisting for a month beyond the

usual course of an acute disease or a reasonable time for an injury to heal. Merskey and Bogduk (1996) defines chronicity in more precise terms as pain which has persisted for three months or longer and it is this definition which is currently accepted in research. Time factors in isolation can be misleading since chronic pain is not simply a persistence of acute pain. Fundamental differences exist in underlying pathology, symptoms, treatment response and management

Acute pain generally has an identifiable cause and sudden onset provoked by noxious stimuli as a result of local tissue damage from injury or disease, (Cousins, 1999, Carr and Goudas,1999). Stimulation of the autonomic nervous system causes anxiety or fear, which serves as a protective mechanism to seek assistance and take appropriate action to aid healing. Pain is therefore usually a symptom of an underlying pathological process most frequently inflammation, 85% (Peterson and Milgrom, 1989).

Diagnosis of the underlying cause of pain is hence the basis of successful treatment with a good response to analgesics. 90% of acute pain will resolve within 4 to 12 weeks irrespective of professional medical intervention (Nachemson, 1982). Reparative healing can occur without medication and pain report ceases before healing is complete. Medical intervention however may be useful to reduce pain by shortening the duration of the injury and speeding up the healing process (Loser and Melzack, 1999).

Chronic pain in contrast is more difficult to define since onset may be insidious with often no clearly identifiable pathology. It serves no obvious function often socially and psychologically destructive with vegetative signs of depression. Pain may appear to occur spontaneously or more commonly originates from an initial noxious stimuli but persist long after the event perpetuated and intensified by other factors. This transition from an

acute to a chronic condition may follow an injury that exceeds the healing capabilities of the body or as a result of damage or alteration to the nervous system. Certain pain may be destined for chronicity from the outset ignoring time factors but related instead to aetiology and the bodies' initial reaction to the noxious stimuli. In attempting to achieve homeostasis after an acute event the stress of pain involves genetically determined neuronal, hormonal, immunological and behavioral activities (Chrousos, 1992). Pain duration is not the distinguishing feature in chronic pain but the body's inability to restore normal homeostatic levels of physiological function (Loeser and Melzack, 1999).

Identifying those patients likely to develop chronicity or preventing conversion from acute to chronic requires investigation. This would be beneficial not only to the patient but to health care services since it is suggested that the 10% of chronic pain sufferers consume 85% of costs associated with pain and sequelae (Linton, 1998). Early intervention for acute pain may in some situations prevent development of chronic disability (Linton, Hellsing, Anderson, 1993).

Demographic and psychological factors have been shown to be predictive of chronicity in several studies but results are inconsistent and provide only a preliminary overview of issues (Turk, 1997). Neurophysiological changes of plasticity at a cellular and molecular level are known to contribute to persistent pain (Doubell,Mannion and Woolf, 1999). Inflammatory mediators in the inflammatory process are associated with sustained peripheral sensitization of nociceptors (Steen et al, 1996). Following injury to the peripheral nerves or dorsal horn neurons following inflammation or trauma alterations occur in the dorsal root ganglion (Ma and Woolf, 1996; Hokfelt et al 1994). In addition a range of psychological factors influence pain modulation.

It is inappropriate to treat chronic pain as neglected acute pain as this can cause iatrogenic damage. Relief of pain symptoms takes priority since underlying pathology may be unclear. Pain perception often remains despite intervention and psychological approaches are required to alter the overall effect of pain on daily life.

Melzack (1998) suggests the brain may be capable of modifying pain information processing to minimize the impact of pain on the individual. Nociception is interpreted and perceived in a manner that diminishes suffering and pain behaviour.

1.3.3 Suffering

"Suffering occurs when the physical or psychological integrity of the person is threatened" (Cassell, 1982). Not all suffering is caused by pain but other negative responses such as fear, anxiety, stress, emotional loss and psychological status. The language of pain is used to describe suffering irrespective of cause and is therefore misleading (Loeser and Melzack, 1999). Amplification or distortion of the patients' experience of pain and suffering can occur through maladaptive behavioral processes (Reesor and Craig, 1988).

1.3.4.Pain behaviour

Pain behaviour is an outward manifestation of the inner subjective self (Horn and Munafo, 1997). It is influenced by a host of factors which include: accepted behaviour within a cultural environment; social modelling; learning, memory and past experience; pain threshold, perception and tolerance and cognitive factors of coping, control, self efficacy and motivation. For instance, ethnicity, beliefs and attitudes amongst cultures are known to effect displays of pain behaviour and pain reporting (Skevington, 1995).Others observe

the behavioural actions or avoidance of actions by an individual. These observations in addition to the individual history and physical examination reflect to the outside world the existence of pain and suffering.

1.3.5. The clinician's role in empathizing with the pain patient

Pain is personal and as such it is impossible to know exactly what someone else feels. Although we may try hard to empathise with the sufferer, in our attempt to understand the problem, it is sheer arrogance to presume we can measure and know what the other individual is experiencing. We cannot see or hear through their eyes or ears nor have we experienced life in the conscious world from their perspective.

Huxley,1946 wrote " I can sympathise with people's pains but not with their pleasures. There is something curiously boring about somebody else's happiness" This seems a very negative view of the inability of an individual to appreciate happieness. Could it be that he empathises with those who are depressed or who find difficulty in shifting from a negative to a more positive frame of mind, chronic pain patients for instance. A depressed pain patient may be able to sympathise with another depressed pain patient and discuss their misery yet almost envy happiness in others. Interestingly with time and patience one could envisage that the same patient, when treated in a positive manner, may begin to assume a more cheerful countenance and eventually start to appreciate the good in life. An effective clinician might therefore, be someone who is sensitive to the patient's negative mood yet has the ability to draw on their own reserves to convey and engender positivity.

Empathetic listening and vicarious learning although helpful in appreciating our patient's concerns and providing appropriate therapy requires large reserves of energy. In order to

retain the level of energy required for sensitive empathising, the clinician may need to be sufficiently detached to care effectively, for the benefit of both patient and clinician. Only by doing this can one hope to analyse, measure and treat pain in a more objective manner.

1.4 Measurement of Pain

1.4.1 Can pain be measured?

Pain and suffering is immeasurable. A multifaceted phenomenon one cannot underestimate the complexity of the human mind in pursuit of accurate scientific measurement. In the objective, systematic assessment of pain acute pain studies must focus on need and effectiveness of treatment analysis whilst chronic pain studies focus on the effect on function progress and outcome of therapy.

Technically the multiple dynamics of pain do not fit into a simple numerical construct and assumptions of relationships between depression and pain or intensity and distress can be problematical. Measurement tools investigating a single dimension of pain are limited. Measures obtained from multiple sources at least provide a broader view of the overall problem, (Williams and Keefe, 1991) The outward expression of pain behaviour is only a public manifestation of the inner experience of pain. Consequently, the observation, self report and attempt at physiologcial correlates is the only aid to understanding the experience. For practical purposes it is sometimes assumed that outward expression and inner experience are indistinguishable (Bates, 1987). This stems from the observation that sociocultural influence affects the perceptual component of pain and outward expression. Syrjala and Chapman (1984), takes this concept a stage further and provides evidence of the relationship between pain behaviour and experience. When patients were requested to

exaggerate facial expressions of pain, subject self reports of pain and autonomic physiological measures of response increased whilst inhibiting facial expressions of pain, autonomic and self reported pain responses decreased. They suggested expressive pain behaviour modulates both physiological components and subjective pain experience in a self-regulatory manner. If one stops concentrating on reading for a moment and smiles broadly (although feeling rather foolish smiling at nothing in particular) is it not true to say that one immediately feels more positive. Could it be that by our public behavioural display of cheerfulness is altering our general affect or mood. Facial expression coding has been employed in experimental studies but requires development in the clinical setting (Craig et al, 1992). In depression corrugator muscle change is hard to suppress and careful observation of facial expression may assist in determining patient exaggeration or masking of underlying pain (Poole and Craig, 1992).

Chapman 1984, disputes the concept of pain as a private experience but suggests that although pain is multidimensional it is a pattern of behaviour increasingly measured, studied and clinically controlled, objective rather than subjective.

1.4.2 The measurement of pain

To study pain scientifically it is essential to attempt some form of measurement, quantification and categorization to allow comparison of scores and statistical analysis. The different dimensions of pain to be measured may be physiological, sensory, affective, behavioural, cognitive and impaction on life. Whilst measurement refers to qualifying a specific element of pain, assessment examines an interaction of factors on the experience of pain (McGrath and Unruh, 1987)

Measures determine location, magnitude or intensity, quality of pain, duration and frequency in aiding and establishing mechanisms and differential diagnosis, to assist in choice of therapy in establishing relative efficacy of treatment.

Measures must be reliable, valid and sensitive. Reliability ensures test retest internal consistency; validity ensures congruency with other measures or observations denoting pain sensitivity indicating a precise reflection of magnitude and change in measurement. With simple scales reliability may exist at the expense of sensitivity. However, some measures may generate quantifiable data amenable to multivariate analysis. The global implications of a pain condition can be investigated in terms of intensity, related disability and depression with alteration in attention, behaviour, thought processes and non-specific physical symptoms (Dworkin ,1992).

1.4.3 Measurement and Assessment tools and techniques

These can be classified into: self – report scales, observational techniques and physiological techniques.

The three dimensions of the pain experience considered most relevant to investigate are intensity, location and affect (Jensen and Karoly, 1991). Pain intensity is a quantitative estimate of pain severity whilst a diagram is used to indicate location. Pain affect denotes emotional arousal and disruption engendered by the experience of pain with various dimensions requiring measurement of multiple items (Jensen and Karoly, 1991).

1.4.4 Self reporting pain scales

Self report pain rating scales range from simple methods to gain information of pain intensity with regard to pain and analgesia to the more complex structural questionnaire or

interview, to incorporate numerous variables including coping skills and functional restrictions.

1.4.5 **Simple pain rating scales:**

There are three simple rating scales: Visual analogue scale (VAS), Numerical rating scale (NRS), Verbal rating scale (VRS). VAS, NRS and VRS are simple, quick, effective, reproducible and valid measures for use in a hospital clinic to ascertain pain intensity,(Turk and Melzack,2001).

VAS, in the simplest form, is a 10 cm horizontal or vertical line used as an increasing indicator with 'no pain' at one end point and 'worst pain' at the opposing end.

Other aspects of pain have also been assessed using VAS including impact on life.

The individual is requested to make a single mark on the line corresponding to the level of pain. Scoring of the scale is achieved by measuring the distance from the start of the line for instance 'no pain' to the mark. This is in millimetres grading 0 to 100 points or cm's 0 to 10.Early studies showed those completing the scale preferred VAS to 4 or 5 point verbal rating scales (Joyce et al 1975)

In comparison to other simple methods, 4-11% failed to complete the scale accurately, (Jensen et al 1994) It was felt 100 points are too many and that most patients use multiples of 5 or 10 in rating pain, reducing effective points to 11 or 21.However, failure rates are significantly reduced when the measure is explained prior to completion (Wilkie et al, 1990)

Price 1994, reports the measurement properties of the scales are influenced by 3 factors; the length of the line, instructions on usage and specific words used to anchor the end

points. Ogon et al 1996 investigated uniformity of score distribution and sensitivity of the VAS in different orientations and demonstrated higher sensitivity in the horizontal orientation for usual pain intensity.

Syrjala and Chapman 1984 highlighted ease of completion by patients who are ill or with limited language capacity but also oversimplification of the pain experience.

A simple verbal scale is derived from VAS assigning numerical scores 0-3 or 4.

1.4.6 The Mc Gill Pain Questionnaire (MPQ) (Melzack 1975)

This is principally a verbal descriptive scale to examine intensity and quality of pain.

In addition to the descriptive scale there is other information considered necessary for evaluation of pain including an overall PPI 0-5 point verbal scale, words to describe temporal properties and a diagram to illustrate localization of pain.

Initially 102 pain descriptor words obtained from clinical literature were classified by physicians and university graduates into small groups describing different aspects of pain. Three major groups were identified sensory, affective and evaluative and 16 subclasses. (Melzack and Torgerson, 1971) Subclasses were given a descriptive label and consist of similar or related words, synonyms, synonymous meanings or subtle nuances.

4 miscellaneous subclasses were later added due to patients finding the absence of key words. The final classification represented the most meaning full and representative qualitative subclasses.

In the second stage of the study words within each subclass were assigned a pain intensity value using a numerical scale 1-5 from least to worst. Physicicans, students and patients all agreed on the relative position or rank ordering of words but not on the intensity values.

There was a high level of agreement on rank ordering of pain descriptors from those of different cultural, socio-economic and educational backgrounds.

The MPQ was developed as an experimental tool for clinics and research to study the effects of various pain management. The scale can be completed as a five-minute interview or as self-report paper – pencil completion when patients are requested to choose words, which describe their current feelings and sensation.

Three indices are obtained: -

- The number of words chosen (NWC)
- The present pain intensity (PPI)
- The pain-rating index (PRI)

The NWC is a simple count of the number of words chosen from each scale. The PRI is the sum of the rank value of all the word sets. The word in each subclass is valued lowest value 1, for least pain increasing upwards. Each word rank value chosen by the patient is summed to provide a score for sensory, affective, evaluative, miscellaneous and total.

PPI 1-5, none, mild, moderate, severe, very severe. These descriptions were taken from the evaluative category, chosen for representing equal distance on mean ranking interval scales to provide an overall pain intensity specification, (Melzack and Torgerson, 1971)

Sensitivity was considered a potential problem with only 5 categories but studies reveal close correlation with the evaluative score and VAS (Walsh and Leber, 1983)

MPQ provides an insight into qualities of pain experienced characterised by a distinctive selection of words. Consistency is noted in choice of words by patients suffering same or similar pain syndromes. MPQ is hence a potential aid to differential diagnosis. Dubuisson

and Melzack, 1976 first demonstrated this discriminative capacity on 8 known pain syndromes. A multiple group discriminant analysis revealed distinctive verbal descriptors for each pain type. Allen and Weinmann 1982 and Melzack et al 1986 looking at headache and TN versus AFP respectively confirmed the typical pattern of pain associated with different acute and chronic clinical symptoms. Differences in patients with or without demonstrable organic pathology were also demonstrated in patterns of MPQ correlation, (Perry et al 1988,1991) There does not appear to have been any studies to differentiate between Atypical Facial Pain and Temporomandibular disorders.

Gaston – Johansson et al (1990), report subjects of diverse ethnic-cultural and educational backgrounds use similar adjectives to describe commonly used words such as 'pain', 'hurt' and 'ache'. Stability and strong test-re test reliability coefficients were demonstrated for the MPQ (Pearce,1989). Lower coefficients for the actual 20 categories with time can be explained by fluctuation in quality of the same pain with time.Studies reveal the MPQ to be sensitive to pain reduction intervention (Pozehl et al 1995, Briggs 1996, Burchiel et al 1996, Eija et al 1996, Nikolajsen et al 1996 and Tesfaye et al 1996).

1.4.7. The Short form Mc Gill Pain Questionnaire SF-MPQ

This was developed for research purposes when more detail is required than VAS or PPI but when there are clinical time restrictions,(Melzack, 1987).

It consists of 15 representative words from the standard long form category, 11 sensory and 4 affective. Overall pain intensity is provided by an additional PPI and VAS. Words were selected on their frequency of usage by patients suffering from a variety of pains. The word splitting was added as a key word in dental pain (Grushka and Sessle,1984). Each

descriptor is ranked on an intensity scale from 0 to 3 none, mild, moderate, severe. Gagliese and Melzack, 1997 in a study of patients with chronic athritis showed consistency amongst age groups young, middle and elderly in the most frequently chosen pain descriptors and in the frequency of SF-MPQ appropriate completion, although the elderly chose fewer adjectives.

Similar to the long-form, the SF-MPQ may be capable of discriminating amongst different pain syndromes and has been used in a variety of studies on chronic and acute pain including response to medical intervention.(al Balawi et al, 1996, Gagliese and Melzak, 1997, Thomas et al 1995 Burchhardt et al 1992 Dudgeon et al 1992). High correlation exists between the SF-MPQ and the LF-MPQ major PRI indices (sensory (S) affective (A) and total (T) with sensitivity to clinical changes following therapy such as analgesic drugs and TENS (Melzak, 1987).

1.4.8 Physiological measures

Utilizing our earlier definition of pain, it is clear that observable, physical markers of disease activity and tissue damage are not necessarily analogous with the experience of pain, (Merskey and Bogduk, 1996). Clinical and radiographic signs of presumed pathology and assumed clinical significance can occur in asymptomatic individuals (Westesson et al, 1989) Pathological indicators used alone as evidence of pain can therefore invoke unnecessary treatment and patient anxiety.

Physiological, autonomic and endocrine activity are associated with pain, particularly marked in situations of acute noxious stimuli, or trauma (Cousins, 1999) In arthritis, joint swelling and inflammation is often visible, in migraine pupil dilation may occur whilst

skin flushing and epiphora may be observed in cluster headaches. However, presence or absence of signs is not indicative of pain.

More frequently measured physiological parameters of pain include: cardiovascular function; heart rate, blood flow and pressure, palmar sweating, respiratory ventilation rate, electromyographic activity of the musculature, electrodermal activity of skin conductance and resistance, thermography for skin temperature and neuroimaging of brain activity. Skin temperature measured using thermography indicates heat in the acute inflammation of arthritic conditions and decreased temperatuire in conditions of altered sympathetic nervous system activity.

Autonomic reflex activity in acute pain can cause catecholamine release increasing blood pressure, cardiac output and ventilation rate causing distress and fear.

Self report of the physiological responses associated with pain have been attempted to negate the problems of direct physical measurement (McCracken, 1992) Sweating, palpitations, dizzieness or faintness have been studied in relation to the fear and anxiety of pain. Fear implicated in the maintenance of pain behaviour and activity avoidance was investigated using the Pain Anxiety Symptoms Scale (PASS). This examines a composite of physiological, behavioural and cognitive items in chronic pain patients which correlates with measures of anxiety and disability. Report of physiological symptoms only represents gross changes but has been shown to be a useful instrument in assessing pain related fear.

Autonomic activity is controlled by a range of internal and external stimuli, is difficult to quantify and may fluctuate despite constant pain. Similarly amongst infants and children the physiological indices of distress; heart rate, respiratory rate and palmar sweating are

evident but not specific to noxious painful procedures since similar responses also occur in novel or nonnoxios stressful events (Hester,1995) Generally, autonomic changes are therefore considered an unreliable indicator of clinical pain since changes may be indistinguishable form those of the general stress response. B endorphin secreation is linked to both acute pain and stress resulting in a decrease in pain intensity. Plasma endorphin concentration is therefore a good indicator of pain modulation but not of nociception (Szyfelbein,1985, Bonica,2001).

In persistent chronic pain, physiological responses may habituate with time (Graceley,1989b).Trophic changes may occur, altered vasomotor and sudomotor activity of the skin , enhanced pilomotor segmental reflex and subcutaneous trophoedematous changes (Gunn,1978).

Electromyographic (EMG) recordings of static and dynamic muscle activity with careful electrode placement has proved useful but often provide inconsistent data in relation to patient reported pain (Watson et al, 1997, Bushnall et al 2000)Measurement reliability and validity is technique dependant varying between surface electrodes, needles or fine wires.(Mohl and Crow, 1993). In facial musculature; age, sex, facial type , subcutaneous fat thickness and tooth grinding were all factors considered to affect diagnostic validity (Widmer,1990,Mohl,1990).

Radiography to quantify pathological signs using plain views, CT and MRI is inappropriate since it generally does not correlate to pain intensity and frequently produces false positive and negative signs.(Boden et al 1990, Jensen et al 1994c)

Brain activity in pain has been recorded using EEG and neuroimaging studies with SPECT (single photon emission computed tomography), PET and MRI, (Flor, 1992, Chen, 1993b,

Casey and Minoshima,1997.) Functional neuroimaging has seen rapid research development in the past 10 years revealing great potential, but currently remains too complex to be a clinical measurement tool, requiring specialist equipment, technical expertise and skilled interpretation of images (Davis,2000, Flor, 2003, Whalley et al 2004)

1.4.9.**Psychological measures**

Three major psychological dimensions of pain were proposed, (Melzak and Casey, 1968).

1) sensory – discriminative

2) motivational – affective

3) cognitive – evaluative

Melzak and Casey, 1968, proposed physiological systems within the brain related to 3 dimensions, sensory by rapidly conducting spinal systems, affective by reticular and limbic activity influenced mainly by slowly conducting spinal systems, discriminative and motivational by higher CNS processes. Interaction of these categories provides perceptual, motivational and cognitive information, which in turn could influence motor response in the complex pattern of pain (Melzak and Katz, 1999)

Turk et al 1985 identified four groups of pain behaviour.

1) distorted ambulation or posture

2) negative affect

3) facial/audible expressions of distress

4) avoidance of activity

Vlaeyen et al 1987 further characterised pain patients by three dimensions suggesting treatment should be guided by patient's location within a construct.

1) withdrawl- approach

2) high arousal – low arousal

3) visible- audible

For instance, relaxation training may be more appropriate for the high arousal patient. This approach to assessment relies on classification of behavioural types and expression of suffering. It is concerned principally with identification and abolition of maladaptive behaviour patterns. Self reported pain and investigating a range of behavioural patterns, coping skills, adaptation and function attributes and meaning has been shown more useful examining therapeutic interventions. Fordyce, 1984, has explored what constitutes pain behaviour. Non-reinforcement of maladaptive pain behaviours by operant conditioning of chronic pain patients was devised by Fordyce, 1984. Treatment proved effective in reducing not only associated disability but also pain intensity (Fordyce et al1985)

The concept of what constitutes pain behaviour continues. Pain behaviour may be interpreted as an outward manifestation of the inner subjective state. However, in this context pain behaviour is considered as a set of indicators of pain and suffering in order to elicit help, appropriate in acute stages of pain but eventually maladaptive when maintained long-term by operant conditioning.

Objective and systematic assessment of pain is required in both acute and chronic pain to ensure appropriate therapeutic intervention.

Karoly 1985 suggest overall aims of chronic pain assessment are to inform and guide, intervention, in four main areas.

1) To determine patient readiness for treatment

2) To prioritise the focus of intervention

3) To quantify the disruptiveness of the problem

4) To assess nature and impact of patient's implicit pain theory

1.5 Concepts of pain

The theoretical concepts and components of pain are gradually unravelled. Attempts are made to measure and understand the multidimensional phenomenon yet still one is left wondering. Acute pain can serve a protective function but why do people experience chronic pain? In some respects, chronic pain could now be viewed as a disease entity. A combination of a neurodegenerative disease due to genetic and pathophysiological changes of the nervous system,(Scholz and Woolf, 2006): in addition an environmental disease with regards to the individuals' internal and external environment, (Cousins,2005).

Perhaps from a theological perspective we should examine Revelations 21v3-4, "..death shall be no more, neither shall there be mourning nor crying nor pain any more for the former things have passed away." "...There shall be no more pain" and until then, we cannot hope to cure all pain during our lifetime on earth, we can only strive to ease the suffering in the world around us. This sentiment is reiterated in the words of Dr Albert Schweitzer,1953,"Pain is a more common fear than death himself. We must all die but I can save him from days of torture, that is what I feel as my great and ever new privilege" The clinicians role in the management of facial pain is indeed a privilege. If we can alleviate or simply help the patient cope with pain we will have achieved something however small.

CHAPTER II

THE TEMPOROMANDIBULAR JOINT AND TEMPOROMANDIBULAR DISORDERS

ANATOMY, PHYSIOLOGY, PATHOLOGY, TERMINOLOGY, CLASSIFICATION AND EPIDEMIOLOGY

CHAPTER II

2.0 The Temporomandibular joint (TMJ)

In the following chapters, I will now concentrate directly on the study of pain related to the temporomandibular joint (TMJ) and associated muscles. In focusing so intently on a specific anatomical site I shall endeavour not to loose sight of the fact that pain can never be studied in isolation. Whatever the condition, pain is a dynamic, perceptual process affecting the suffering human being in their entirety.

2.0.1 Temporomandibular disorders (TMD)

Pain and dysfunction of the TMJ is the most common chronic orofacial pain condition; yet, with respect to aetiology it is difficult to define and classify accurately.

The current definition of TMD is:

- Pain in the preauricular area, TMJ, or muscles of mastication
- With or without limitation or deviations in mandibular range of motion
- With or without TMJ sounds during jaw function

(Dworkin and Drangsholt, 2005)

In order to understand the disorders of the TMJ one must first appreciate the normal functional anatomy and physiology. Differential diagnoses must be excluded and the condition confirmed by recognition of the reported symptoms and presenting signs, together with a careful history and clinical examination. Terminology and classification are then explored, followed by the epidemiology of the condition, aetiology and management.

CHAPTER II

2.1 ANATOMY

2.1.1 The joints

The bilateral temporomandibular joints form the craniomandibular articulation between the condylar heads of the mandible and the inferior surface of the temporal bones. These two complex, synovial joints permit significant movement between the two bones, each covered with an articular surface and united by a capsule creating a joint cavity filled with synovial fluid. In addition to being synovial, the joints are described as ginglimoarthroidal due to the articular surfaces being seperated by an interposed articular disc, (Okeson,1996). This creates superior and inferior joint compartments, allowing hinge and translatory movements respectively.

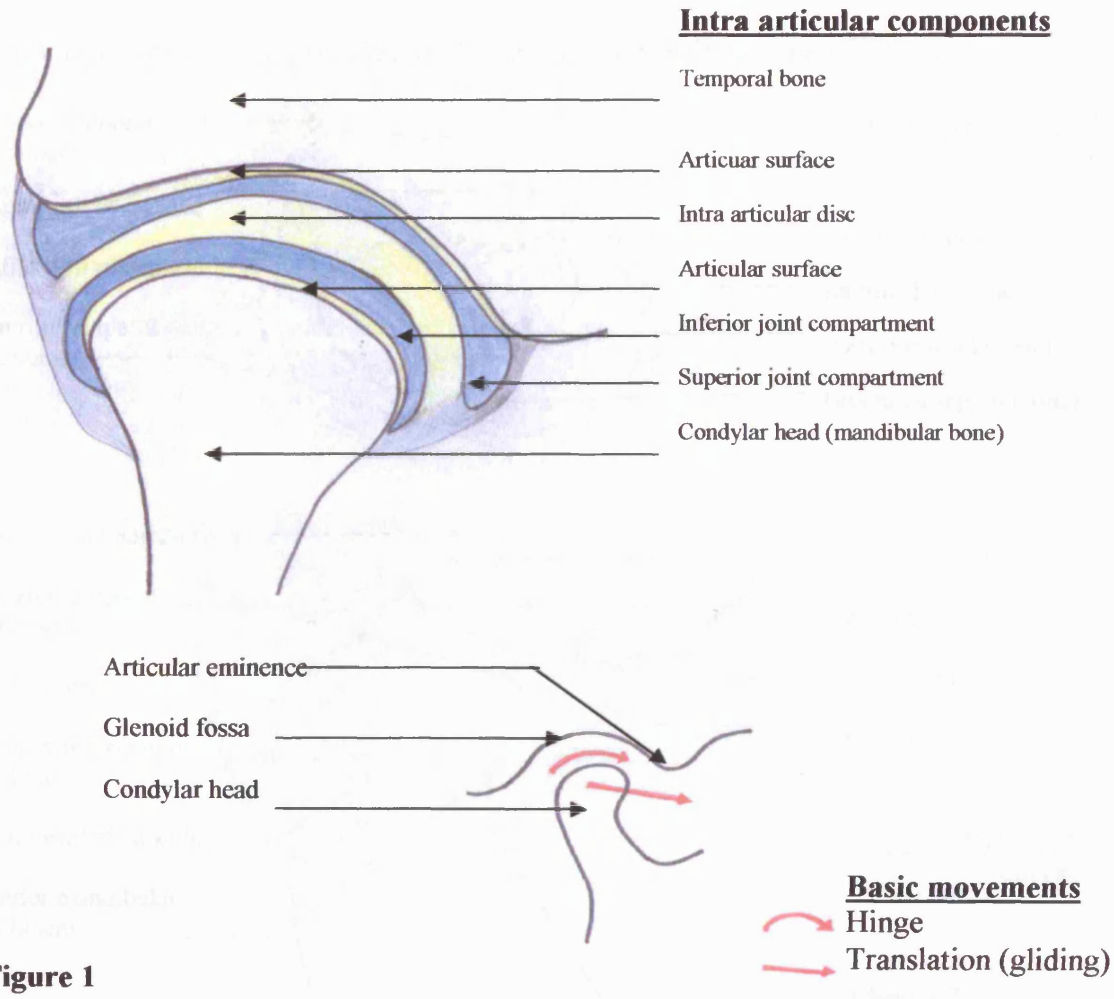


Figure 1

2.1.2 The joint components

2.1.2.1 Bone structure

The head of the condyle, glenoid or condylar fossa and articular eminence or tubercle are the boney components of the joint. Each are covered on the articular surface by fibrous connective tissue not the hyaline cartilage seen generally in synovial joints,(Norman et al,1990). This may have unusual reparative implications,(Meikle,1992).A scattered arrangement of cartilage cells within the condylar head, also ensures an ability to modify and remodel the shape allowing adaptation to functional stress,(Ten Cate,1998, Avery, 2000).

2.1.2.2 Disc

Composed of dense fibrous connective tissue, pear shaped, non uniform in thickness with four distinct zones, thinnest in the central intermediate zone,(Williams,1999).

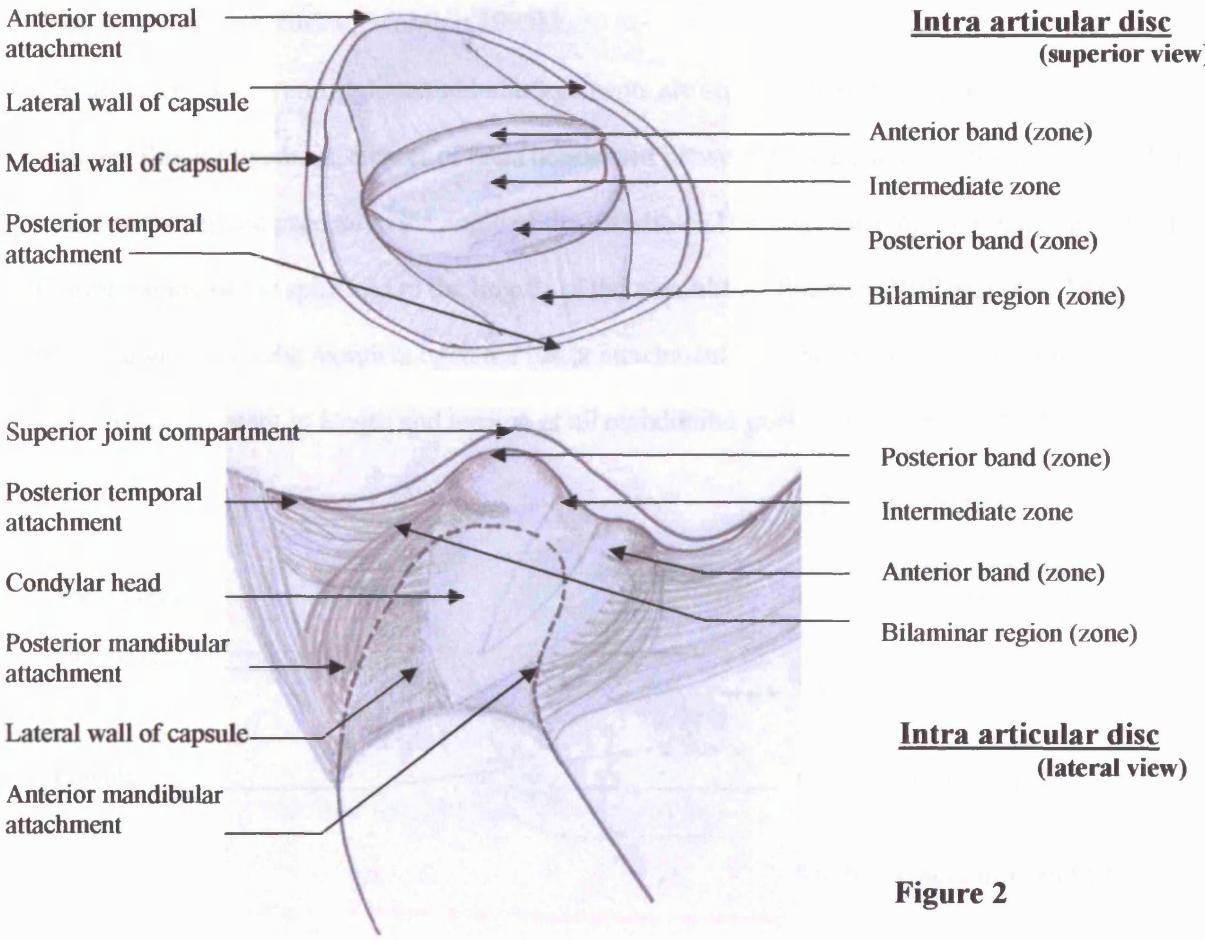


Figure 2

2.1.2.3 **Capsule and synovium**

The fibrous capsule enclosing the intra articular components is lined by synovial membrane. Within this membrane synovial cells in the lymphatic capillaries of the villi produce synovial fluid to bathe the joint surface,(Griffin and Sharpe,1960).On average there is 1.2ml of fluid in the superior joint space and 0.9ml in the inferior joint space,(Toller,1974). Alterations to quantity and viscosity of synovial fluid influencing normal joint function or creating a vacuum effect have been suggested, (Nitzan et al,1992) However, the mechanics of joint turbology still require further investigation,(Nitzan et al,2001,2004)

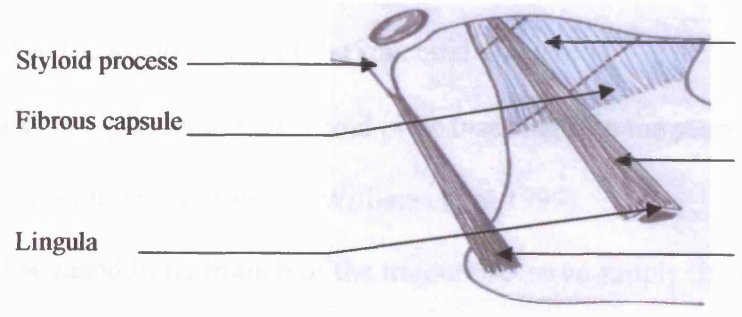
2.1.2.4 **Ligaments**

Laterally the capsule is strengthened by the fibrous band of the lateral temporomandibular ligament. This runs obliquely downwards and backwards from the zygomatic arch to the lateral posterior border of the mandibular neck. Relaxed at mandibular rest position but tightened in jaw protrusion,(McMinn,1995).

The accessory sheno and stylo mandibular ligaments are separate from the capsule. The stylomandibular ligament, a sheet of facia condensed between the carotid and submandibular glands connects the styloid process to the angle of the mandible. The sphenomandibular ligament extends from the spine of the sphenoid to the lingula of the mandibular foramen,(Williams et al,1989). Interestingly, when the mouth is open the lower attachment is at the axis of rotation of the mandible and remains constant in length and tension at all mandibular positions,(McMinn,1995)

Figure 3

TMJ ligaments

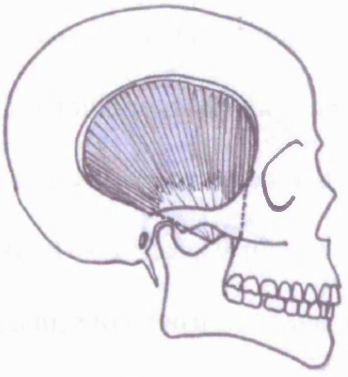


Medial aspect of mandible.

2.1.2.5 **Muscles of mastication**

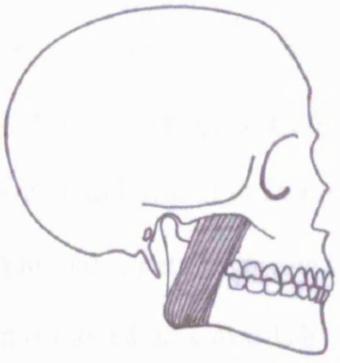
The principal muscles associated with the joints are the bilateral temporalis, masseter, medial and lateral pterygoids.

Figure 4: Temporalis



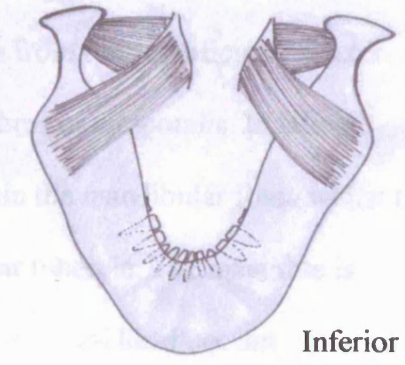
The broad temporalis muscle has almost horizontal posterior fibres and vertical anterior fibres, superficial and deep heads converge to a central tendon inserted on the coronoid process. The muscle is covered by a sheet of fibrous temporal facia roofing over the temporal fossa,(Johnson and Moore,1997).

Figure 5: Masseter



The masseter, composed of three layers originates from the zygomatic arch to insert into the ramus and angle of the mandible,(Johnson and Moore,1997).

Figure 6: Pterygoids



Inferior view of the mandible

The medial pterygoid originates from the medial aspect of the lateral pterygoid plate and small area of the maxillary tuberosity to insert into the inferior surface of the ramus and the angle of the mandible.Whilst the lateral pterygoid originates from the greater wing of the sphenoid and lateral aspect of the lateral pterygoid plate inserting into the pterygoid fovea,anterior neck of the condyle and capsule,(Williams et al,1999).

The mandibular branch of the trigeminal nerve supply the musculature and the joint.

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2.2 PHYSIOLOGY – Static and dynamic function

The action of jaw muscles are combined to allow complex movement. Individual muscle contribution can be analysed by EMG activity placing electrodes on or over muscles to monitor electrical activity,(Ferguson,1988).

Mandibular movements can be defined as hinge and translation which combine to produce functional depression (opening), elevation (closing), protrusion, retrusion and lateral excursion,(Williams et al,1989). Functional movements in turn combine to produce the dynamic movements of eating, composed of incision and chewing cycles. The rapid and complex jaw movements require precise neural control demonstrated to some extent by the jaw reflexes,(Fergusson,1988).

Elevation or closing of the mandible is produced by the contraction of the temporalis, masseter and medial pterygoid. Depression or jaw opening is achieved by hinge and gliding movement. The lateral pterygoid pulls the condylar head forward whilst the chin is moved downwards by the infra and supra hyoid muscles, principally the digastric. In protrusion, lateral pterygoid pulls the condylar head and the articular disc forward along the articular tubercle with contribution from the superficial masseter. Retrusion is principally achieved by the horizontal fibres of temporalis. In lateral movement the ipsilateral condylar head remains within the mandibular fossa whilst the contralateral head is translated forward on the articular tubercle. The mandible is rotated about a vertical axis passing just behind the ipsilateral head not through it so consequently the head makes a small lateral movement called Bennett shift,(McMinn,1995). Jaw movement can be examined during clinical examination to observe limitations and dysfunction.

2.3 PATHOLOGY

Pathological alteration to the joint can result from a variety of causes;

1) Congenital,developmental (aplasia, hypoplasia, hyperplasia)

2) Neoplastic disorders (benign and malignant)

3) Trauma (Intracapsular and extracapsular)

4) Ankylosis (Intracapsular, extracapsular,boney and non boney)

5) Arthritides (Inflammatory, Infective , Degenerative)

6) Musculoskeletal disorders.

Musculoskeletal disorders may present as pain and dysfunction, related to arthralgia (joint pain), mylagia (muscle pain) and internal derangement of the joint. Internal derangement is a result of uncoordinated movement of the intra articular components with resultant clicking, sticking or locking of the joint, with or without pain.
TMJ pain related to the musculoskeletal system is the most common non infective, pain condition of the orofacial region, (Lipton et al,1983, Dworkin et al,1983). The diagnosis is dependant on presenting signs and symptoms, history and examination.

2.4 Temporomandibular joint pain and dysfunction

2.4.1 Diagnosis

The lack of any objective diagnostic tests, such as tissue biopsy to differentiate those with or without the condition, is a similar situation to other musculoskeletal pain, (Lund,1995,Widmer,1995).Other diagnostic techniques; including jaw tracking devices, thermography, sonography and electromyographic (EMG) analysis of masticatory muscle activity are not reliable indicators for diagnosis, (Laskin and

Greene,1990,Widmer et al, 1990, Mohl et al,1990).A careful history, examination and use of selective imaging is currently the best substitute available,(Lund et al, 1995).

2.4.2 History

The pain history in the form of presenting complaints and history of presenting complaints, medical, family and social history provide the essential key to the diagnosis, (Feinmann et al,1984, Speculand et al, 1984).This important concept will be more fully appreciated when considering the aetiology of the condition in Chapter 3. The history itself is complimented by the clinical and radiographic examination.

2.4.3 Clinical examination

Clinical examination includes a standard inspection of the hands, face and posture; cervical examination including swellings and lymphadenopathy; neurological examination and intra oral examination of the dentition and soft tissues. The specialised examination of the TMJ aims to investigate joint and muscle tenderness, limitation in mandibular movement , joint sounds and functional occlusion.

2.4.3.1 Palpation of joints and muscles

Reported pain or tenderness in usually assessed by the application of pressure to specific anatomical sites. Pressure is usually applied with the ventral aspect of the index finger or both index and middle fingers with a standard pressure for 3-5 seconds. The mandible should be in a position where the teeth are clenched then slightly apart to avoid active muscle contraction. Joint palpation is achieved by positioning a finger in the preauricular region,anterior to the tragus of the ear, to locate the lateral pole of the condylar head. A finger placed into the external auditory meatus, with mouth

opening, allows palpation of the posterior aspect of the condylar head.(Dworkin et al,1990)

The associated muscles are palpated for pain and in addition swelling, hypertrophy, atrophy and symmetrical contraction, (Clarke et al,1989). Sites of tenderness vary within the same muscle of an individual patient so the entire muscle should be palpated. Temporalis anterior and posterior fibres; origin, body and insertion of masseter are the simplest and most reliable muscles to palpate. Additional sites included in the examination are the submandibular region for medial pterygoid, suprahyoids and anterior digastric; stylohyoid and posterior digastric between sternocleidomastoid and posterior border of the mandible and intra orally temporalis tendon insertion, superior, anterior aspect of coronoid and lateral pterygoid in the posterior lateral aspect of the maxilla,(Ohrbach,1999).

Interexaminer reliability (0.4-0.6 acceptable agreement, 0.6-1 good agreement) (Petrie and Sabin,2003) was investigated for palpation sites in several studies. Dworkin et al,1988, found 0.47 for extra oral muscles, 0.27 for intra oral muscles and 0.47 for the TMJ, similar findings to Goulet and Clark,1990. At present an alternative is to consider muscle palpation tenderness as a single composite score for all muscle groups consequently producing higher reliability (Dworkin et al,1988, Fricton and Schiffman,1986 and Dworkin et al,1990)

A pressure algometer is an instrument used for quantified measurement of pressure pain threshold. It indicates that tenderness remains relatively stable for minutes to hours as a valid diagnostic sign but becomes less stable over time and response may vary within the same day,(Orbach and Gale,1989.)Pressure pain threshold scores to discriminate patients from non patients or for use in differential diagnosis is currently not feasible.

Factors affecting reliability of patient response to palpation include the amount and duration of pressure applied and exact location of palpation site. Confounding factors will affect reported pain including culture,age, gender and pain duration. For epidemiological studies an optimal pressure of 0.9kg for extra oral muscles and 0.45kg for intraoral muscles and TMJ sperate patients from non patients (Dworkin et al,1990). Clinical studies however have shown optimal pressure to vary dependant on the different muscles examined ranging from an optimal $2kg/cm^2$ for superficial masseter and 3.1 kg/cm^2 for temporalis body (Goulet and Clark,1990.) Physiological and psychological factors including; patient's affective state at the time of the examination, sensitization of peripheral nociceptors or second order neurones, altered thalamic processing, perceptual and neurological measures will influence patient response, (Ohrbach,1998).

For clinical purposes joint and muscle palpation should be adapted to the individual patient and to the specific muscle region, (Orbach and Gale,1989).

2.4.3.2 **Limitation in mandibular movement**

Evaluation of mandibular movements includes the vertical opening,closing range and movement pattern together with horizontal lateral and protrusive excursions,(Clark et al,1986).

The opening range of motion can include pain free, unassisted maximal and assisted maximal opening. All three measurements have excellent inter examiner reliability (Kappa 0.9-0.98) and provide relatively stable results over short periods of time, (Widmer et al, 1992). Distances are measured using a mm ruler from the incisal margin of the maxillary incisor to the opposing mandibular central incisor. A

calibrated mm ruler is considered adequate for measurement so increased precision with electronic instrumentation is not warranted, (Ohrbach, 1999).

Establishing values for normal and abnormal mouth opening is debatable. Goulet and Clark,1990, calculated the odds ratio of patients having a pain free opening less than 45mm to be 3:1. This high cut off has sensitivity of 79% and specificity of 71% so few patients will have a mouth opening greater than 45mm but some non patients will open less than 45mm. Patients with a presumed average mouth opening may report this to be much less than normal. Absolute values will be dependant on interindividual variation particularly relating to gender, body size, age and clinical history.

In one study males average mouth opening was around 52.9mm and females 49.4mm differing by 3.5mm and in another males 47.9mm and females 45.4mm varying by 2.5mm (Dworkin et al,1990)

Determination of horizontal excursive movements and vertical opening patterns; straight, corrected and uncorrected deviations are also examined. The midline or mid sagittal reference point is located on maxillary and mandibular incisors and for horizontal movement a mm ruler used to assess extent of lateral movement. Inter examiner reliability is less than the vertical measure,(Kappa 0.7),(Dworkin et al 1990).This is partly because jaw movement and pattern improves with practice (Clark et al,1989) In protrusion, measurement of deviation and deflection are even less reliable,(Widmer,1992).

2.4.3.3 **Joint sounds**

Auscultation and palpation of the TMJ is used to distinguish the presence of joint sounds. Alone, this is not considered a reliable diagnostic tool compared to joint and muscle palpation or mandibular movement, (Pollman,1980, Mohl,1999).

CHAPTER II

Within the asymptomatic population the prevelance of any joint sounds is reported to be about 34% (Dworkin et al,1990,Gross and Gale,1983). Single or multiple sounds can also vary in character from one assessment to the next, appear and disappear.(Dworkin et al,1988,Truelove et al ,1987,Dworkin et al, 1990)

Clicking and crepitus are however reliably distinguishable from one another, (Clark et al, 1989,Dworkin et al,1990, Goulet and Clark,1990 ,Webeke et al,1989). Crepitus occurs in cases of arthrosis whilst causes of clicking are variable and are defined in table 1. Moderate diagnostic validity has been achieved in the diagnosis of internal derangement clicking, sensitivity 0.78 and specificity 0.52, whilst diagnosis of crepitus in arthrosis has a sensitivity of only 0.4 but a specificity of 0.9, (Paesani et al, 1992).

Amongst techniques employed to determine joint sounds,finger palpation is the preferred clinical method, improving diagnostic specificity although lowering sensitivity, (Widmer,1992) Instruments such as the stethoscope are capable of detecting more subtle sounds. These sounds are not considered diagnostically meaningful and in addition discrimination of pathological versus normal mechanical sounds are consequently more difficult to determine,.(Dworkin et al,1988,Dworkin et al,1990).

Electronic sonography recording TMJ sounds for later characterisation has not been found to be advantageous due to surrounding sound contamination (Mohl et al,1990, Widmer,1989, Widmer et al ,1990 and Gallo et al,1991)

Joint noises or clicking may be present without pain and are then often considered a benign nuisance or social embarrassment more than a debilitating ailment. However, when pain is present on clicking, elimination of pain is the main objective. Unfortunately for the patient, joint sounds may remain unchanged despite the improvement in pain post treatment (Ohrbach and Dworkin,1998).

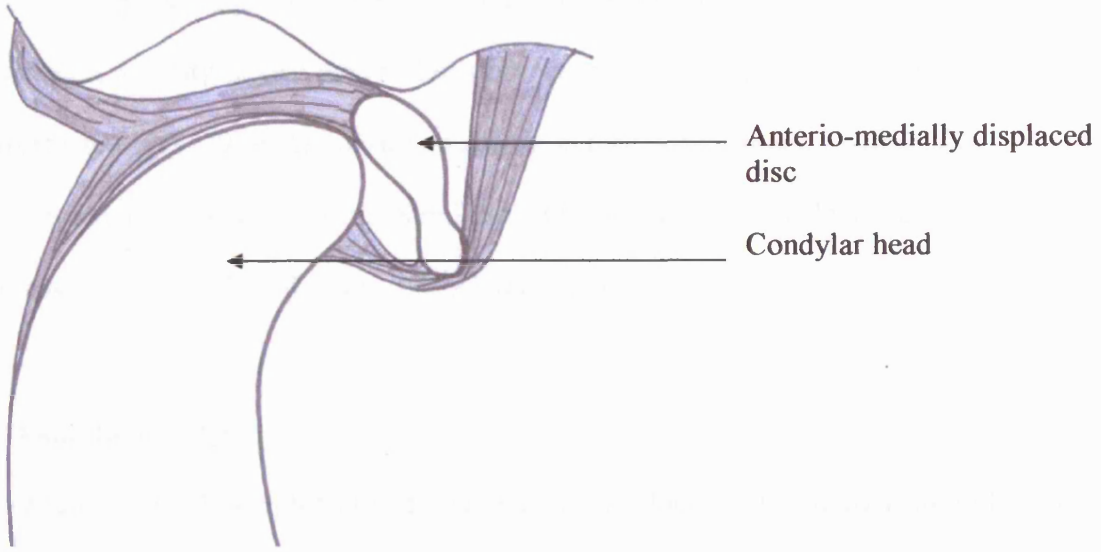
Kleinberg,(1991) clearly defined causes of TMJ clicking as outlined in table 1.

Table 1: Causes of clicking

DYSFUNCTION	CAUSE
1) Click associated with deviation in form of condyle, disc and temporal fossa	Mechanical obstruction to condylar translation might arise from morphologic changes and remodeling of articular surfacesand disc perforations.
2) Click associated with neuromuscular dysfunction	Uncoordinated movement of the TMJ disc may be due to dysfunction of the controlling musculature.
3) Eminence click	Associated with forced joint opening and with a protrusive opening arc.
4)Click with anterior disc displacement	Anterior displacement of the disc in the joint space causes a click to occur as the condylar head moves across the posterior ridge of the disc This occurs on mouth opening and closing producing a reciprocal or double click.. This may progress to closed lock when the condylar head is unable to pass the posterior ridge, resulting in limitation of mouth opening.
5)Click associated with hypermobility	Condylar head clicks over anterior ridge of disc with wide mouth opening.
6)Tethered disc click	Posterior disc attachment damaged as a result of trauma may prevent normal translation of the TMJ disc on mouth opening. Reciprocal click may occur as the condylar head passes over the anterior band of the meniscus on opening and closing of the mouth. **(Klineberg,1991).**

Reducible anterior disc displacement is the clicking condition most frequently encountered

Figure 7: TMJ disc displacement



2.4.4 **Further investigations**

2.4.4.1 **Radiographic examination and imaging techniques**

In conjunction with clinical history and examination, imaging of the TMJ may provide additional information with regards to joint pathology or differential diagnosis. Indications for imaging are dependant on positive examination findings and history suggestive of recent and or progressive pathology, (McNeill,1990) .

Intra oral radiographs may be necessary to exclude specific dental disease whilst an orthopantomograph provides an overview of the dentition, maxillary sinuses and gross joint structure. An appreciation of the broad variation in normal appearance is necessary to recognise joint abnormalities (Aquilino et al,1985, Dixon et al,1984, Drace and Enzman,1990.) However, osseous changes are often not detectable on radiological examination and intraarticular derangements are not visible, hence diagnosis remains mostly dependent on clinical judgement, (Westesson,1985).

Larheim, 1995, advocates CT for TMJ hard tissue imaging in selected cases where pathological lesions such as tumours are suspected. MRI has replaced arthrography as the imaging technique to determine internal derangements (Rao, 1995).There are however, indications that pain and dysfunction may be independent of disc position. Westesson et al, 1989, demonstrated abnormal disc displacement in 15% of asymptomatic healthy controls. Similarly, 50% of patients with closed lock were found to have normally shaped discs, (Nitzan and Dolwick, 1991).

2.4.4.2 Blood tests

In addition to radiographic or imaging techniques, blood tests ranging from full blood count and erythrocyte sedimentation rate, antinuclear antibodies, latex fixation tests and serum uric acid may be appropriate in specific cases to exclude or confirm systemic disorders and differential diagnoses, (Ohrbach,1999).

Having established a diagnosis, the name given to the condition varies considerably.

2.5 Terminology - TMJ pain and dysfunction

Terminology , a tedious technicality or an essential directive? Confusion and disparity in opinion regarding aeitiology is evident in the abundance of names ascribed to the painful condition affecting the TMJ joint and associated muscles. More than a dozen names have been introduced since Costen first described "a syndrome of ear and sinus symptoms dependent upon disturbed function of the TMJ"(Costen 1934).He described a staggering 14 different symptoms and despite new avenues of thought it has been the symptomatology of the condition not the aetiology which has remained the focus for labelling the condition.

Early names include Costen's syndrome, replaced by the Temperomandibular joint

pain dysfunction syndrome(Schwartz,1956), the Myofascial pain dysfunction syndrome(Laskin,1969) .The Temporomandibular pain dysfunction syndrome (Molin,1973) and Tempromandibular joint dysfunction syndrome (Toller,1974) Historically , the condition had become categorized as a syndrome suggesting exclusive signs and symptoms. Facial arthromyalgia (FAM) avoids the term 'syndrome' and was introduced as a far more sensible descriptive term which can be easily explained to the patient.(Harris,1974)

Meanwhile, the presumed source of pain ossilated between the muscles and the joint, reflected in the emphasis in choice of terms TMJ or myofascial. Descriptive terms in Germany included "occlusomandibular disturbance" and "myoarthropathy of the TMJ",(cited by Okeson and Lexington,1997)."Temporomandibular joint disturbances" were replaced by "functional TMJ disturbances"(Ramjford and Ash,1971). The definition of internal derangement of the TMJ justified separating TMJ dysfunction from the more generalized myofascial pains.

In contrast, broader more collective terms were then introduced to include symptoms not necessarily related directly to the TMJ with the use of the term Cranomandibular disorders,(Mc Neill,1983).In 1986, the IASP combined temporomandibular pain dysfunction and tension headache under the same broad category of 'craniofacial pain of musculoskeletal origin,(Merskey,1986).TMJ pain as a localised symptom of a more generalised condition such as fibromyalgia has also been suggested, (Blasberg and Chalmers,1989,Wolfe et al ,1992,Plesch et al,1996).

The American Academy of Orofacial Pain and the American Dental Association Presidents Conference on examination, diagnosis and management of temporomandibular disorders recommended that orofacial pain and mandibular dysfunction be termed TMD(Temporomandibular disorders),(Bell,1982). This is a

broad term, encompassing specific and nonspecific clinical disorders related to the TMJ and functional disturbances of the masticatory system.

TMD has been categorized as:-

-Pain in the TMJ region or muscles of mastication.

-Limitation or deviation in mandibular range of motion.

-TMJ sounds during jaw function. (American Dental Association,1983)

The term is synonymous with craniomandibular disorders and facial arthromyalgia. The term acknowledges that symptoms of the TMJ may arise as a result of numerous related disorders rather than a single entity or syndrome and that some patients may have multiple disorders of varying aetiology and pathology.

In some respects such a broad collective term is perhaps too diffuse and needs refining to exclude obvious pathology which may otherwise mask aetiology and impede our further understanding of the remainder of the conditions. I would favour the introduction of a further term; Temporomandibular Arthromyalgia(TMAM). Derived from the precise term FAM but emphasizing the identity with the broader term of TMD. This would categorize the as yet non specific joint internal derangement disorders and the associated myofacial pain and dysfunction disorders into acute and chronic, related specifically to the TMJ. However, this would add yet a further dimension or burden to the already over subscribed collection of terms!

I shall refer to TMD as the internationally recognised inclusive term for TMJ pain and dysfunction ,although I shall in fact restrict my studies to the subcategory of TMAM.

In order to communicate effectively within a profession a universal label, or interchangeable labels, must first be agreed upon. We must then ensure we are all discussing the same condition and here the role of classification is of paramount importance.

Table 2: TMJ diagnostic classification – the main systems introduced over the past 50 years	
Introduced by:-	**Form of classification:-**
Weinmann and Sicher, 1951	Three groups: (a) Vitamin deficiencies, (b) Endocrine disorders, (c) Arthritis
Schwartz, 1959	Distinguished (a) Organic joint disorders (b) Masticatory muscle disorders
Bell, 1960	Six groups divided by (a) Intracapsular (joint disorders) (b) Extracapsular muscle disorders
Farrar, 1972	Eight clinical areas of dysfunction a)masticatory muscle hyperactivity b) decreased range of mandibular motion secondary to degenerative joint disease c) muscle incoordination d) anterior dislocation of the disc e) capsulitis f) synovitis g) loose capsular ligaments h) strained capsular ligaments
Helkimo, 1974	Two indices (a) Ai - An amnestic dysfunction index (self report) (b) Di – Clinical dysfunction index (clinical examination)
Block, 1980	A broad system based on anatomy and aetiology of pain in the head, neck and shoulders,in accordance with rheumatology and neurology
AAOP(American Academy of Orofacial Pain) McNeil et al, 1980	Grouped into functional disorders of the masticatory system (Craniomandibular TMJ disorders)
ADA (American Dental Association), Griffiths, 1983	Five categories described TMD (Tempromandibular disorders) introduced by Bell
Eversole and Machado, 1985	Simplified taxonomy..Myofacial pain dysfunction separated from TMJ internal derangement..Recognised overlap of signs and symptoms in myogenous and arthrogenous conditions. Hierarchical scheme.
IASP (International Association for the Study of Pain) 1986	Medical multidimensional classification of pain disorders which included category III craniofacial pain of musculoskeletal origin with two subcategories: (i)Temporomandibular pain and dysfunction syndrome (ii)Osteoarthritis of the TMJ Five axes: (a)Regions,(b)Systems (c)Temporal characteristics of pain: pattern of occurence (d)patients statement of intensity:time since onset of pain (e) aetiology
CMI (The Craniomandibular Index) Fricton and Schiffman, 1986	Continous scales categorizing degree of severity in multiple domains including (a) Muscle palpation index (MPI) (b) Muscle dysfunction index (MDI) (c) Total symptom severity index (SSI).

IHC (International headache classification) World Health Organization , Okeson ,1988.	Thirteen categories of headache. (Inclusive consideration of all head pain) 11th category: headache or facial pain associated with disorders of cranium, neck, eyes, nose, sinuses, teeth, mouth or other facial / cranial structures.No elaboration on specific subcategories related to TMJ and masticatory muscle disorders are included. Okesson proposed classification for TMJ, additions to the IHC A minimum of five episodes of pain in the temporomandibular region,with at least two of the following four clinical signs 1) increased myofacial tenderness 2) restricted opening 3) disk displacement 4) signs of arthritis or arthrosis.Subdivided into episodic less than 6-12 months or chronic more than 6-12 months.
Stegenga et al, 1989	Provided insight into intracapsular disorders a)Articular:Inflammatory,Noninflammatory b) Nonarticular disorders Osteoarthritis and Internal derangement divided according to staging over time
AACD (American Academy of Craniomandibular disorders) 1990	Two main groups (a) joint disorders (b) muscle disorders, integrating TMD into the broader context of head,neck and facial pain by utilising and expanding category 11 of the IHS classification system.
AAHNFP and TMJO (American Academy of Head, Neck, Facial Pain and TMJ Orthopedics), Talley et al,1990	Five TMD categories, two nonTMD categories Nineteen subcategories under the main category of myofaical disorders separated by the specific tendon or muscle involved
ICCMO (International College of Cranio-Mandibular Orthopaedics Bergamini and Prayer-Galetti,1990	Three groups: I – Presence of oclusal flags, II – Musculoskeletal disorders associated with myofacial trigger points of the head and neck, III – Organic osteoarticular damage of musculoskeleton of the head and neck.
Truelove et al, 1992	Multiple diagnostic joint and muscle groups. (Non hierarchical) Operational criteria determining type and severity of the disorder
Research Diagnostic Criteria RDC/TMD Dworkin and le Resche, 1992	Formalised dual diagnosis (Non hierarchical,operationalised criteria) Axis I- Physical condition (3 groups – wih a possible 8 diagnoses) (a) muscles disorders, (b) disc displacements, (b) arthralgia, arthritis, arthrosis Axis II – Psychosocial issues (Global severity of pain, disability and depression)
AAOFP (American Academy of Orofacial Pain), Mc Neil 1993	Specific TMD subcategories to be included in 11th category of IHS classification
AAOFP (American Academy of Orofacial Pain) Okesson,1995	Updated subcategories of TMD for 11th category of HIS classification
The TMJ scale, Levitt,1994	Global scale with contributions from scales for pain report, joint dysfunction, palpation pain, stress, chronicity and psychological factors Developed for use in Dental practice.Based on self report findings rather than examination but attempted to classify psychological factors and pain impact.
AAOFP (American Academy of Orofacial Pain),1996	TMD subcategories provided as input for the IHS classification Non hierarchical.

2.6 Classification – TMJ pain and dysfunction

Taxonomy, to classify disease, represents a construct or set of constructs. These are developed to clarify a plethora of available information and in turn require evaluation to ensure validity and reliability, specificity and sensitivity, (Dworkin and LeResche,1992).

Ideally the system for TMD should be comparable to those of other chronic pain conditions and be useful to researcher, clinician and ultimately benefit the patient. Classification of TMD is instrumental to our further understanding of aetiology, natural history, prognosis and treatment, yet impeded by the same lack of knowledge. (Dworkin and Le Resche, 1992). This conundrum of TMD classification initiated a broad field of exploration which still continues after nearly half a century of dedicated research.

Classification systems over the years have utilized a variety of parameters to group the disorders according to: signs and symptoms, anatomical or functional sites; presumed aetiology; pathophysiology or a mixture of parameters. Some are hierarchical in character or context assessing severity of the condition .Others assign subjects to multiple categories and are non hierarchical continuous or even global rating scales which attempt to incorporate a measure of pain impact and psychological functioning.

Table 2 gives a brief summary of some of the main classification systems introduced over the past 50 years.

Most classification systems have been designed for epidemiological research. Helkimo, 1974, completed a cross sectional population based epidemiological study of TMD using one of the first developed classification systems of jaw pain severity

and dysfunction. Two separate indices were developed "An amnestic dysfunction index Ai" based on self report and the "Clinical dysfunction index Di" based on clinical examination. These indices have since been employed in over 100 epidemiological studies yet reliability, validity and utility of indices remain untested(Van der Weele and Dibbets, 1987).

Rugh and Solberg,1985, Katz,1985 identified development of a uniform classification system as an essential element in the study of TMD and this was discussed at the National Institute of Health Technology Assessment, 1996.

A group of international investigators collaborated in the design of The Research Diagnostic Criteria for TMD (RDC/TMD) a currently reliable taxanomic system for classifying the subtypes of TMD using a dual axis system to measure two dimensions of TMD pain,(Dworkin and LeResche,1992).

Axis I

Axis I investigates the physical component using standardised clinical examination and a few self report questions to establish clinical diagnosis.

Group I - Muscle disorders (Myalgia) (a)Myofascial pain (b) Myofascial pain without limited opening (c) Myofacial pain with limited opening

Group II – Disc displacements (a) with reduction (b) without reduction with limited opening (c) without reduction without limited opening

Group III – Arthralgia,arthritis,arthrosis (a) Arthralgia (b) Osteoarthritis of the TMJ (c) Osteoarthrosis of the TMJ

Axis II

Axis II explores psychosocial status of distress and dysfunction associated with TMD,based on standardised psychometric instruments. The global severity of the condition is considered incorporating pain intensity, disability, depression and non-

specific symptoms.

It has been suggested that it may be more appropriate to seperate orofacial disability into a third axis (Turk et al 1995) There was also concern the dual axis system derived theoretically may not reflect the true patient population with TMD. However, initial reliability and clinical utility of the multiaxial system appears favourable (Garofalo et al, 1998, Ohrbach and Dworkin 1998)

An alternative multiaxial approach of classifying psychosocial status involves identifying patient profiles or subgroups using an empirically derived approach, Turk and Rudy,1987. Similar to The RDC/TMD a clinical diagnosis is made and then a multiaxial assessment of pain (MAP) classifies chronic pain patients by integrating psychosocial and behavioural data. Using the MPI, recurring patterns of data appear to represent homogenous subgroups. Cluster analysis on the MPI scales in chronic pain patients identified three patient groups, dysfunctional, interpersonally distressed and adaptive copers, (Turk and Rudy,1990). This has been repeated in further chronic pain studies by Talo (1992) and Jamieson et al.(1994) . Rudy et al,1989, specifically examined TMD and again identified these three clustered groups. Each group were independent of age, pain chronicity and general TMD symptoms of palpable muscle pain, limited mouth opening and joint sounds or CT examination. The identification of these subgroups is an interesting concept. When comparing TMD to head pain and low back pain all diagnostic groups are represented in the three MAP subgroups. Pain disorders in different anatomical sites and arising from disparate causes have been found to respond to similar treatments,(Woolf,2004).Similarities between chronic pain patients may be more pertinent than the diagnostic groups themselves. This may have implications in tailoring treatment to reflect the psychological profile of the patient rather than the physical factors, (Turk et al, 1996). Rudy et al, 1995, reminds us that

TMD cannot be understood by psychological indicators alone. Woda et al,2005, developed an interesting taxonomy of idiopathic orofacial pain and found similarities between Facial arthromylgia (TMD) and Atypical facial pain using psychological and physical parameters. Currently clinical and radiographic markers do not relate to any particular psychosocial or behavioural variable and TMD subgroups cannot be clearly determined on behavioural patterns. Despite much progress in this field, the need for a unified classification system still exists, Bryant and Sessle,1995. The challenge of classifying physical and psychological diagnoses therefore remains in order to identify appropriate management for the physical and psychological characteristics of each patient, (Turk et al, 1996).

Subcategories with common signs and symptoms are likely to respond to similar treatment but from a clinical perspective it is unnecessary to further subdivide groups if they can be managed by the same therapy. Subcategories are useful from a research perspective but in certain situations it is necessary to establish a general cohort of individuals with overall signs and symptoms of TMD.

Drangsholt and Le Resche,1999, highlight the concept that most classification systems miss the essential ingredient of a simple question or questions to classify prescence or absence of musculoskeletal TMD pain. Specific questions regarding TMD were examined for validity amongst a group of Canadian patients. They used nine questions relating to TMD pain at rest and on function, finding 75% sensitivity and 75% specificity for two or more positive responses compared to the Helkimo clinical index. Macfarlane, 2004 in an epidemiological study used a self-completed questionnaire to predict the most likely specific orofacial pain syndrome. Widmer, 1995, used written questionnaires and telephone interviews to identify individuals with TMD. When results were compared with the findings on clinical examination 82% of cases had

been correctly calssified. The same question slightly modified in format was used in the RDC. " Do you have pain in or around your jaw joint in the muscles of your face or in your ears at rest." A reliable and valid set of questions to include the identification of subcategories, accepted internationally, has yet to be developed which can replace a thorough history, physical and radiographic examination.

2.7 Epidemiology – TMJ pain and dysfunction

2.7.1 - Epidemiological studies-Prevalence

Many studies have attempted to determine prevalence of TMD but the now accepted methods of epidemiological research have not always been adhered to.

Inadequate sample size or non representative samples of a population were commonly encountered as well as no age or gender specific proportions given, no spread or dispersion data and no report on subgroups. Case definitions often did not include pain or were dependant on physical examination and are not explicit of severity or duration. Drangshot and Le Resche, 1999, using multiple searching methods to look at the past 30 years literature, identified 196 of which 133 English language studies exist of cross sectional and cohort studies reporting signs and symptom prevalance of TMD, published as original research in peer reviewed journals. Excluding studies assessing only signs, non painful symptoms, compound problems or examining selected populations43 studies remained, 34 in adults and 9 in juveniles.

These were then grouped into TMJ categories of ambient pain or unspecified (rest or rest and function) and functional pain (on jaw opening and clicking).

2.7.2 Prevalance of functional TMD.

16 population based studies report gender specific prevalence of functional TMD over a range of 2-6%. Prevalance amongst females was generally higher but female to male

ratio ranged from 0.67 and 4.0. A comparison of functional versus ambient pain within the same studies revealed a higher ambient prevalence of about 70%.

2.7.3 **Prevalance of ambient or unspecified TMD.**

13 population based studies reported prevalence of ambient or unspecified TMD in males to range from 0-10% and in females 2-18%. Female to male gender ratio ranged from 1.2 to 2.6 but most studies reporting a 2 to 1 ratio. Studies reporting on age relationship revealed a varied pattern but none resembled the exponential increase in prevalence with age seen in chronic disabling conditions such as Rheumatoid arthritis. In early studies there appeared little or no change with age (Helkimo,1976). Lipton et al 1993, Matsuka et al 1996, found an inverse relationship of pain declining with increasing age. Agerberg and Bergenholtz 1989, showed the reverse, that pain increased with age, whilst normal distribution with greatest prevalance around 25 - 54 years was found by (Dworkin et al 1990, Goulet et al 1995.)

2.7.4 **Seasonal alterations in TMD.**

One study investigated the effect of seasons on TMD pain and showed amongst 136 female subjects a small but statistically significant increase in pain during the winter months (Gallagher et al 1995, Raphael and Marbach 1992a,b).Further studies on seasonal relationship may give rise to an unknown aetiology.

2.7.5 **Diurnal variation**

Goulet et al 1995 and Dao et al 1994 showed increased pain symptoms as the day progressed. In a small case controlled study however, daily pain patterns were found to differ for bruxing and myofacial pain patients. Bruxing patients reported morning pain whilst myofacial pain increased as the day progressed (Dao et al 1998).

2.7.6 Global effect of TMD

TMD is a common condition. 1 in 3 adults develop TMD during their lifetime (Dworkin and Le Resche, 1993). 10% of women and 6% of men are affected each year which in the USA amounts to 20 million adult cases per annum. Assuming similar proportions across cultures would give a population prevalence of 450 million adults world-wide (Dragsholt and Le Resche, 1999).

2.7.7 Health Care

Drangsholt and Le Resche, 1999, reviewing demand for TMD treatment revealed that from 11 studies 2-7.5% of the population in North America and Scandanavia had sought treatment for TMD during their lifetime. Estimating ¼ - 1/3 of persons with TMD pain during a year seek treatment, 50-75% of patients 1st visit a dentist, the remainder a physician (Glaros et al, 1995, Turp et al 1998).

Incorrect or delayed diagnosis and referral were found in several studies of both dentists and physicians (Foreman et al 1994, Glaros 1995). This is not thought to indicate a lack of interest or training in the condition but may reflect the controversy which exists over treatment (von Korff et al 1988).

The first clinician visit usually determines subsequent referral, dentists refer to dentists, physicians to other physicians (Foremen et al 1994 and Glaros 1995).

Alternative medicine is also sought, when pain does not respond to traditional treatment but this is not included in surveys of overall treatment cost. (Turp 1998), Foreman et al 1994).

2.7.8 Race

Only two studies report measurable differences in TMD between racial groups.

Khan 1990 reported rural African countries to have a lower proportion of TMD pain than found in North America and Europe but difference may be related to research methods and definition of TMD.

Lipton et al 1993 showed slightly lower prevalence of jaw joint and facial pain in African Americans compared to white Americans but this was not adjusted for SES or gender.

Wildmalm et al 1995 in a small cross sectional study of 4-6 year olds, in contrast, showed a higher proportion of self reported TMD in African American children but again did not adjust for SES or possible difference in ethnic interpretation of questions.

Studies to compare developed and developing countries with or without social health care systems have been proposed but a universally accepted case definition has first to be established for TMD with similar meaning across languages (Moore and Dworkin, 1988).

2.7.9 **Individual patient considerations**

TMD shares many important features with other chronic pain conditions with regard to psychological distress and individual burden (Dworkin, 1995).

Five different chronic pain conditions : TMD, back pain, severe headache, chest pains and abdominal pain were compared in 1,016 people from an HMO population based cross sectional cohort study.

TMD chronic pain had similar individual impact and 'burden' as the other 4 pain conditions with comparable pain severity, duration, inability to undertake activities because of pain, psychological distress (anxiety, depression, somatization) and major depression (von Korff et al 1988a).

Negative impact on an individual has been reported in several non population clinic studies. A 1/3rd of TMJ chronic pain centre patients reported disturbed sleep, depression and a less satisfying life than previously (Murray et al, 1996). A rather extreme life impact was recorded from a TMD pain support group where patients reported spending Can$ 30,000 on treatment, losing job, home belongings and remaining in persistent pain (Garro et al 1994).

Despite these rather extreme figures it is estimated TMD does place a significant burden on a ¼ of affected individuals, at a time of individual peak productivity (aged 20-50).

2.7.10 **Economic considerations**

TMD as a economic cost to society has been divided into :-

(i) Direct costs of health care provision

(ii) Indirect costs due to work disruption, loss or decreased productivity. (Lipton and Stewart, 1997)

Direct cost has been estimated in 2 studies examining annual cost of speciality TMD health care per patient in the USA. (Shimshak et al 1997) showed inpatient costs of US$935 and outpatient costs of US$1,738 per year within an HMO not including psychiatric care, outside the HMO. These figures were double the costs of all the other HMO members. von Korff 1995, from data available from a more cost efficient HMO estimate a more conservative US$304 not including intra oral appliance production.

In 1990, a national dental survey of occlusal appliance production, mainly used to treat TMD was calculated to cost US$990 million a year. This represented 2.9% of the dental services total US expenditure for the year (Pierce et al 1995).

An estimate of annual cost would be around 2 billion, assuming 5.3 million people present annually with TMD at a minimal cost estimate of US$400 per person per year (Drangsholt and Le Resche, 1999).

Indirect costs ultimately have an economic effect on society. Such figures are presently unknown but are likely to be much greater than direct costs as shown in migraine studies (Lipton and Stewart,1997). Unemployment and decreased work effectiveness has been investigated. Unemployment was found to be 5 times higher than the regional average when "high disability" and "severe limitation" was reported by 28.6% of TMD patients similar to figures for back pain 26.6% and severe headache 22.2% (von Korff 1992).

Decreased efficiency at work was reported by 64% of selected myofacial pain patients compared to 7.7% of patients with non painful bruxisim (Dao et al 1994).

Work interference was reported by 26.1% of patients referred to a cranio facial pain unit (Murray 1996).

An age and gender specific pattern similar to migraine, namely female predominance over the age range 15-50 was only indicated in two studies, (von Korff et al 1988a and Goulet et al 1995).

2.7.11 Children and Adolescent TMD Pain Prevalence

2.7.11.1 Ambient TMD pain

9 studies of self report pain prevalence up to the age of 18 were around 2-6%.

Estimates ranged from 0.7% in 11-16 year olds (Sieber et al 1997) up to 18.6% in 12 year old Finish children (Heikenheimo et al 1989).

Four of the studies were gender specific but female and male prevalence ratios were between 0.5 and 2.0 indicating no consistency in reporting of pain by gender.List et

al,1999, Drangsholt,2005 report TMD related pain to be more common in females than males.

2.7.11.2 **Functional TMD Pain**

12 studies report pain with jaw function overall ranging from 0.2-12%.

Prevalence differences before and after puberty could not be compared since prevalence was not usually analysed by age. A number of studies that did report results separately above and below the age of 14 showed an increase (Brandt 1985, Heikenheimo et al 1989 and Motegi et al 1992) one showed a decrease (Nilner and Lassing 1981) and others reported no discernable difference, with age. (Kitai et al 1997).

In conclusion to the prevalence studies, signs and symptoms of TMD are observed in childhood but increase in severity and frequency in young adults, appearing twice as frequently in adult females as in males and decling into old age.

2.7.11.3 **Analytic epidemiological studies of Incidence**

To calculate incidence, a cohort of subjects without the disorder must be followed over time. 20 cohort studies on TMD have been published but 13 do not report TMD pain as a measure, (Drangsholt and Le Resche,1999).

Three cohort studies do report the incidence of TMD pain or give enough data to calculate incidence figures of 1.6%-3.9% per year, (Kitai et al 1997, von Korff et al 1993, Heikinheimo et al 1990).

Incidence in relation to age is currently unknown. Only one study has reported incidence in females which was higher (von Korff et al 1993).

CHAPTER II

Incidence data will eventually be able to show how many people and at what age they develop symptoms. Obstacles to such information are numerous, the time and expense involved in following a sufficiently large group of people without a history of TMD over a relatively long time interval with frequent queries is the main problem in establishing sufficient power to detect an effective answer. Only one cohort study had sufficient numbers 1,016 to measure the low incidence rates around 2-3 new cases per 100 persons per year (von Korff 1993).

Cumming et al 1990 indicate epidemiological methods are under development for studying recurrent conditions like TMD where initial onset may occur early in life with recurrent episodes differing in pain location, character and severity.

The interpretation of incidence rates for episodic and recurring disorders, as noted for other chronic musculo skeletal problems is difficult (Lawrence et al 1998) This could be extrapolated to TMD and perhaps makes interpretation of results ambiguous.

Certainly in longtitudinal studies, the majority of TMD showed fluctuation in report of signs and symptoms during the follow up (Kitai et al 1997).

CHAPTER III

TEMPOROMANDIBULAR DISORDERS

AETIOLOGY

CHAPTER III

3.0 AETIOLOGY

3.1 Introduction- The controversial field of TMD

The aetiology and management of TMD has been one of the most contentious areas of dentistry over the past 50 years causing immense polarization of views (Molin,1999). Concepts have ranged from the mechanistic occlusal theories to the increasingly accepted biopsychosocial concepts which encompass a more holistic approach to management and suggest a multifactorial aetiology.

3.1.1 Historical perspective - Is TMD a relatively new ailment?

The ancient Egyptian technique of repositioning a dislocated jaw is reiterated by the ancient Greeks who describe techniques still used today (cited in Shwartz,1959). This is often quoted as evidence that TMD is an ancient condition with dislocation being an advanced feature of muscle tension and disturbed TMJ coordination constituting TMD,(Molin,1999).However, dislocation of the TMJ can result from a variety of reasons and it does not seem totally improbable that dislocation may have resulted from a purely physiological forced mouth opening and or psychological reasons unrelated to TMD.

From an anthropological view point ancient skulls can be shown to exhibit extreme occlusal wear. This could be interpreted as excessive parafunctional bruxism due to the life and death stresses of ancient civilization resulting in TMD or perhaps more feasibly as a dietary consequence of eating unrefined foods.

Not until the beginning of the 19th Century does any writing re-emerge relating to problems of the TMJ. It is perhaps no coincidence that dentistry too was in a stage of rapid progress. New materials and techniques were being developed for prostheses and hence the study of mandibular movement, occlusion and any effect on the TMJ

were under close scrutiny. In 1918, Prentiss an anatomist and his dental colleague Summa reported lesions in the TMJ from a study of dental conditions in human cadavers. They proposed the lesions to have occurred from defective bites causing excessive load on the joints (Prentiss,1918).

The masticatory system is a beautifully crafted feat of architecture and structural engineering. A dual ginglymoarthroidal joint enmeshed by intricately woven ligaments and muscles and balanced by an interdigitating occlusion. Each tooth itself a sculptured landscape of mountains and valleys. It is not difficult at this point in the literature to appreciate the logical concern that might arise regarding the iatrogenic damage imposed by altering the occlusion. Dental treatment, restorative or prosthetic could never hope to attain the perfection of a natural dentition. This could only be aspired towards years later by damage limitation with the introduction of prophylactic fluoride, conservative management and where intervention is required with ever more sophisticated biocompatible materials.

It would seem that it was the preoccupation with occlusion per se that was the major mistake. The preconceived 'ideal' occlusion was considered a desirable if not essential prerequisite for an healthy masticatory system. An iatrogenically damaged occlusion was not simply in need of further restoration but the natural dentition was also under scrutiny. Malocclusion, in some cases, prophylactically treated to prevent the development of TMD.

The occurrence of occlusal disturbance in the natural dentition was vastly over estimated . Clarke, 1982, comments that "the masticatory system must either be unique in the body's evolutionary development in its failure to fulfill its function properly or else our comprehension of the system has mistakenly led us to describe as abnormalities conditions that in fact may be normal and play no role in bruxism and

TMD." Examining the occlusion in more detail I will now examine the evidence, if indeed it exists, for the role of the anatomy in TMD aetiology.

3.2 Aetiological factors - Anatomical structure

The biomechanical structures, which have been implicated in aetiology, are related both to the occlusion and the musculature and boney skeleton. Changes in the teeth are answerable in the muscles and muscular changes subsequently answerable in the jaw.

3.2.1 Occlusion

Historically, occlusal variation was perceived as the principle aetiological factor for TMD. Now the occlusal role is less clear and most associations appear to occur secondary to joint alterations and increasing age, (Pullinger et al, 1993). To comprehend occlusal impact the static, dynamic, functional and Para functional components of occlusion require analysis both in isolation and in combination.

3.2.1.1 Static occlusal relations

3.2.1.1.1 Loss of posterior occlusal support

Reduction in occluso vertical dimension (OVD)

This is one of the oldest theories of TMJ disturbance dating back to Costen, 1934. Nearly 60 years later, animal studies suggest raised OVD causes rapid morphological adaptive response in the TMJ (Rashed and Sharawy, 1993).

However, reviews indicate that moderate changes in OVD (4-6mm) do not cause TMD symptoms or masticatory muscle hyperactivity,(Rivera-Morales and Mohl, 1991).Lost molar support was correlated with boney changes in the TMJ's in skull studies, (Whittaker et al, 1985). Similar findings were also recorded from osteoarthritic change,

(Alkerman et al, 1988, Tegelberg and Kopp, 1987, Holmlund et al, 1989). However, these subjects were not necessarily in discomfort. It is unclear whether individuals are more likely to develop signs of TMJ osteoarthritis because of lost posterior teeth or that posterior tooth loss is correlated with increased age and increased likelihood of osteoarthrosis development. When age is controlled as a confounding factor the association between osteoarthrotic change and number of teeth is lost, (Whittaker et al, 1990 and Wildmalm et al, 1994).

Loss of 3 to 5 teeth and unequal tooth loss between the left and right sides of the mouth revealed a higher prevalence of TMD than control subjects, (Franks, 1967). However, more recent cross sectional studies of non patient populations provided no evidence of a link between TMD and loss of molars, (Pullinger et al, 1990, Muir and Goss, 1990, Lundeen et al, 1990, Leake et al, 1994, Holmlund and Axelsson, 1994).

3.2.1.1.2 **Cross bite**

Cross bites generally have been shown to be unrelated to TMD, (De Boever and van den Berghe, 1989,Runge et al, 1989, Cachotti et al 1991, Seligman and Pullinger, 1991). However, investigating cross bites in more detail, it is the bilateral anterior or posterior crossbites that are unrelated to TMD. The unilateral maxillary posterior lingual cross bites, occurring in 10% of the adult population, does appear to be more common in TMD patients, (Pullinger et al, 1993). This includes those with non reducing and reducing disc displacement with or without reduction. It has been suggested therefore that in a few cases the adaptive demands on the masticatory system may be at the expense of articular disc adjustment and development of internal derangement, (Pullinger et al, 1993).

These findings support the correction of a unilateral cross bite in children but probably not in adults where skeletal adaptation will already have occurred.

3.2.1.1.3 **Over jet (Horizontal overlap of teeth)**

Increased over jet has been reported to be related both to TMD symptoms and OA change (Tsolka et al, 1994). Most studies do not support the relationship to TMD, (Runge et al,1989, Roberts,1987,Cachiotti et al, 1991). An over jet greater than 6mm is uncommon in the healthy population but has significant association to TMJ disease. Seligman and Pullinger,1991 (shown OJ>5mm v uncommon in a healthy non-patient population). Over jet more than 4mm was linked to OA but not TMJD suggestive that some increased OJ in adults might be secondary to condylar repositioning seen in advanced OA, (Pullinger et al, 1993).

3.2.1.1.4 **Overbite (Vertical overlap of anterior teeth) (OB) and anterior open bite (AOB)**

Reduced OB and skeletal AOB has been associated with condylar changes, (Akerman et al, 1988, Williamson et al,1990,Pullinger and Seligman, 1993).AOB was seen in Rheumatoid arthritis, Osteoarthrosis and myalgia cases but also in those with TMJ internal derangement disorders ,(Helkimo,1974,Tegelberg and Kopp, 1987, Pullinger et al, 1988).Increased OB is generally not associated with TMD , (Heloe et al, 1980, Pederson and Hansen, 1987, Riolo et al,1987, Cachiotti et al, 1991).Runge et al, 1989, relates joint sounds to large OB and masticatory muscle tenderness .

These static occlusal factors found in TMD patients of increased OJ, reduced OB, AOB, unilateral posterior cross bite, occlusal slides >2mm and lack of posterior tooth

contact may be the result of changes in condyle position following intracapsular alteration rather than the cause of the problem, (Vanderas,1994, Juniper, 1994).

3.2.1.2.**Functional occlusal relations**

3.2.1.2.1 **Occlusal guidance**

Teeth provide anterior guidance whilst the TMJ provides posterior guidance on jaw movement. Anterior teeth are generally considered preferable since posterior tooth are considered to cause interferences.

Occlusal guidance patterns on lateral excursion, namely group function or canine guidance has been considered influential in TMD signs and symptoms,(Ingervall et al, 19800.However, the association is not confirmed from other studies, (Bush, 1985, Runge et al, 1989.)

3. 2.1.2.2 **Retruded contact position / Intercuspal position**

(RCP) (centric relation) / (ICP) (centric occlusion)

A slide between RCP and ICP, less than 1mm, is common amongst around 90% of the general population, (Ramjford and Ash, 1983).However, length and direction of slides are influenced by the tooth shape and position. A long or lateral component to the slide is considered more awkward to adapt towards particularly a lateral slide from RCP to ICP, (Solberg et al 1979). Wassell,1989, reports there is no real evidence relating length of slide to TMJ dysfunction. Sagittal slides >2mm were only found amongst TMD groups and those with degenerative change within the TMJ but a slide > 5mm was required to be highly associated with TMD (Pullinger et al, 1993).

3.21.2.3 **Occlusal interferences**

These are tooth contacts, which hinder functional occlusal jaw movement,(Ramjford and Ash,1983). Uneven intercuspal or deflective tooth contacts have been studied particularly in the last 30 years, (Ramjford 1961, Berry and Singh, 1984). Uncordinated dysfunctional muscles or more commonly occlusal discrepancies such as tooth loss, abherent development or poor restorations may cause uneven intercuspal contact. Kampe and Hannerz, 1987, found a higher incidence of sub clinical dysfunction amongst subjects with restorations compared to those with none. Non-working side interferences are believed to have a damaging effect on mandibular movement , (Schillingburg et al, 1981). A non-working side interference combined with a slide from RCP to ICP is more common in TMD patients but did not increase with severity of signs and symptoms, (Mohlin and Kopp, 1978).Deflective contacts and interferences may only be detected in dysfunctional patients when muscles relax with a splint, for example, and the mandible repositions. Effective treatment is therefore required before correct occlusal analysis can be performed. Many studies perform occlusal evaluation whilst subjects are still dysfunctional which therefore renders the findings inaccurate and may account for the variation in reported results. Establishing appropriate and reproducible methods, for assessing accurate occlusal examination of interferences and deflective contacts, is difficult to achieve when overcoming mandibular posturing. Guarding of the neuromuscular system may mask interferences and prematurities. Wearing a stabilization appliance may assist in muscle relaxation and determining the true occlusal interferences. Occlusal evaluation undertaken prior to treatment, whilst patients are still muscularly dysfunctional, will not reveal the true interferences,(Wassell,1989).

CHAPTER III

Occlusal abnormalities in nonpatients cause no dysfunction if they are within the neuromuscular adaptive capacity, (Ramjford and Ash, 1983). The reaction of a patient to the same occlusal abnormality may be affected by distress and emotional problems and may be beyond their normal neuromuscular adaptive capacity, (Wassell 1989). Therefore although occlusal discrepancies are found in most individuals it still remains important to determine whether the occlusion of TMD patients differs in any way from normal subjects.

The relative contribution of occlusal factors has been investigated using logistic regression analysis, (De Laat et al, 1986, Pullinger et al, 1993). 10-25% of specific TMD diagnoses were explained by occlusal variants in adults. Increased OA change and myofacial pain was associated with the following: RCP to ICP slides greater than 2mm, overjet over 6mm and AOB; internal derangements with unilateral maxillary lingual cross bite; internal derangement and OA change with more than 6 missing posterior teeth. Most associations were however deemed secondary to joint alterations,(Pullinger, 1993).

Clark et al, 1997, however, states "the relationship between occlusion and TMD is not convincing, powerful or practical enough to make any recommendations about a causal association." More recent studies again indicate malocclusion is not a significant factor in TMD pathogenesis,(Kitai,1997, Minagi,1997,Goldstein,1999).

Matsumoto,2002, found no statistical difference between two groups of individuals with normal occlusion or malocclusion and concluded a negative association of occlusion to TMD.

3.2.2 Skeletal factors

Genetic, developmental, infectious, traumatic and iatrogenic factors can all result in skeletal malformation, inter and intra arch discrepancies, yet the role of skeletal malformation in TMD is difficult to determine. For instance, there is often an increased prevalence of occlusal interferences associated with malocclusion for instance in Class III deep OB, AOB and cross bite but few reports of increased prevalence of dysfunction, (Egermark- Eriksson et al, 1987).

3.2.2.1 Class II, increased OJ, decreased OB.

Class II division 2 occlusal relationship does not displace the mandible posteriorly, (Demisch et al, 1992). Retrognathia in children is commonly associated with internal derangement of the TMJ with disc displacement but the skeletal abnormality may not be the cause, (Schellhas et al, 1993).

Lobbezzo-Scholte et al, 1995, Hackney et al, 1993, found forward head posture did not increase internal derangement of the TMJ.

A steep or acute articular eminence has been considered an aetiological factor in TMD. It is suggested the small surface area of the eminence gives rise to a larger concentration of occlusal force encouraging OA change, (Nickel and McLaughlin, 1994a).Meanwhile, unilateral joint sounds were found to be more common with the less steep condylar movement path, (Wabeke et al, 1995). Panmekiate et al, 1991, in an arthrographic study found the posterior slope of the TMJ articular eminence to be less prominent where there was anterior disc displacement without reduction, compared to superior disc position and anterior disc displacement with reduction.

3.3 Aetiological factors - Physical Trauma

Force which exceeds normal functional; loading, intensity and duration of the masticatory system, may potentially cause dysfunction and subsequent pathology (Okesson1995).

Physical trauma can broadly be divided into direct and indirect and is more commonly reported in TMD patients than controls (Skolnich et al,1994, Braun et al, 1992, Pullinger and Seligman,1991)

3.3.1 Direct trauma

Direct, macro trauma, such as a blow to the jaw causes an impact injury. Damage ranges from boney fracture to muscular bruising. TMJ structural damage may lead to the cardinal signs of inflammation with loss of function. Tearing of the retrodiscal tissues during trauma is associated with disc displacement disorders (Vichaichalermvong et al 1993). Rest can lead to recovery of this acute phase debility but in some cases permanent damage may occur especially where perpetuating factors delay healing.Burgess,1991, record localised TMD symptoms 24-72 hrs after direct trauma. However, symptom onset arising after the event causes difficulty in establishing the true aetiology (Katzberg et al,1985).

Prolonged or extensive mouth opening when yawning, shouting or unusual stretching, twisting and compressing forces during biting and eating have all been cited as initiating or aggravating TMD (Harkins and Marteney,1985). Iatrogenic trauma from dental procedures or oral intubation for GA need further investigation (Harkins and Marteney,1985,Taylor and Way,1968).

3.3.2.**Indirect trauma**

Cervical hyper extension / hyper flexion injury, commonly referred to as "whiplash" has been reported to cause a higher prevalence of TMD than occurs in a control population particularly when the teeth are apart on impact(Weinberg and Lepointe,1987,Braun et al 1992, Kronn,1993,Ogle and Hertz,2000).

Szabo et al,1994, however showed human volunteers in motor vehicle rear collision impact tests did not reveal jaw movement. Kasch et al, 2002 in a prospective controlled trial of rear collision suggest whiplash is not a major factor in the development of TMD.

Computer modelling also suggests certain motor vehicle injuries, despite flexion-extension events in the neck do not produce similar movement in TMJ (Howard et al,1991). Alternatively, cervical structures injured in acceleration deceleration injuries may give rise to pain in the cervical area which is referred to the trigeminal site, resulting in symptoms of TMD (Szabo et al 1994)

However, a causal relationship between indirect trauma and jaw symptoms has not yet been substantiated and aetiological significance at present remains uncertain (Burgess,1991,Goldberg,1990).

3.3.3 **Microtrauma**

Microtrauma has been used to describe "repetitive-strain" type injury of the TMJ and musculature. These may include parafunctional activity such as: bruxism (non-functional grinding); clenching; lip, finger nail or pencil biting; chewing gum habit or postural imbalances such as: abnormal protrusive jaw posturing, phone bracing, use of snorkelling mouth piece, playing musical instruments or singing.

3.3.4 **Parafunction**

In general it is suggested parafunction does not result in TMD (Marbach,1992, Scholte,1993, Luz and Oliviera,1994). However, it has been suggested particular subgroups of TMD are precipitated or perpetuated by parafunctional habits or abnormal jaw posturing (Rugh,1988,Faulkner,1990ab,Schiffman et al 1992, Nitzan,1994, Dao et al 1994, Attanasio,2000.)Experimentally induced parafunction has been shown to cause pain similar to that reported by TMD patients (Christensen,1975, Moss et al,1984,Scott and Lundeen,1990).

Neurological disease for example cerebral palsy and extra pyramidal conditions including epilepsy and orofacial dyskinesia can cause intense and persistent para function(Fahn,1985). Muscle hyperactivity in relation to emotional distress is mediated via the cortex and hypothalamus (Weiner et al,1993). Stress, anxiety, sleep disorders, medications including neuroleptics, certain elicit drugs and alcohol aggravate intensity and frequency of parafunctional bruxism and cause excessive tooth wear (Rugh,1988, Redfearn et al,1998, Robinson et al,2005). Carlsson,2003, suggests daytime clenching and nocturnal grinding are two separate entities. Interestingly, clenching does not cause NM fatigue, as sustained muscle activity is compensated for by slower firing rates or recruitment of motor neurons (Junge and Clark,1993).The similarly idiopathic tension headache has been shown to be unrelated to muscle tension(Oleson&Jensen1991) Arthrogenous TMJ disorders also do not appear to be associated to muscle hyperactivity(De Leeuw et al,1994).

3.3.5 **Bruxism**

A virtually universal condition in humans, anthropologists believe that bruxism may even be beneficial flattening occlusal surfaces and increasing chewing efficiency

(Varrela,1990). Nocturnal bruxism occurs during light non-REM sleep, regardless of occlusion (Dahlstrom, 1989, Lavigne et al, 1999). In the past, theories related to human bruxism related to muscle over exertion, pain, fatigue and spasm in masticatory muscles resulting in a vicious cycle maintaining and aggravating TMD symptoms mediated through psychological distress, (Laskin,1969). This theory is now considered largely erroneous, Stohler et al,1996. Nevertheless, 60% of individuals with TMD also have a bruxism habit,(Alvarez-Arenal,2002). Interestingly, parafunctional activity and internal distress is seen in animals and the term 'stereotypies' used to describe parafunctional behaviour. In confined spaces cows roll their tongues , tethered pigs bite on their chains, horses crib-bite and dogs chase their tails (Redbo,1992). Antidepressant medication in the form of Prozac given to dogs, chasing their tails, in the USA was found to stop this repetitive activity.

3.3.6 **Attrition and bruxism**

Dental attrition was believed to be the most common marker of bruxism,(Holmgren et al,1993). Yet, comparing TMD patients and asymptomatic controls the severity of observed attrition is indestinguishable (Pullinger and Seligman,1993, Rugh,1992). John,2002, Pergamalian et al,2003 found incisal tooth wear, possibly a consequence of bruxism, was not found to induce TMD and bruxism was not correlated to myalgia. However, attrition may not be representative of an ongoing habit and hence cannot predict current bruxism levels (Dao et al,1994). Attrition appears to occur in bursts due to unspecified factors and is therefore perhaps episodic in nature (Lundh et al,1987, Johansson et al 1993).Erosive diets, eating disorders, occlusal forces, environmental factors, protrusive guidance changes in OB & OJ correlated with age and gender can also influence dental attrition patterns (Silnees et al,1993, Johansson et al,1994,

Waltimo et al,1994). Self report questionnaires or clinical evidence of tooth wear are inadequate measures. Direct measurement using EMG and sleep laboratory may assist in classification of the role of parafunction in TMD and patterns of muscle contraction, (Okesson,1996). Glaros et al, 2004, induced an experimental model of TMD –like symptoms in 3/10 asymptomatic individuals by encouraging jaw clenching and increasing masseter muscle activity through increasing EMG activity through biofeedback. Manfrendi, 2003, found bruxism to be related to muscle disorders rather than joint pathologies.

3.4 **Aetiology - Psychosocial trauma**

Since biblical times the "grinding and gnashing of teeth" depicts an image of a soul in torment. It may well be this associated mental picture of bruxism, pain and emotional turmoil that initially drew clinicians to analyse the role of psychological factors amongst TMD patients.

3.4.1 **Emotional distress , muscle hyperactivity and parafunctional habits**

Schwartz(1955) led a multidisciplinary collaboration which introduced a psychophysiological model for TMD. The team psychiatrist regarded parafunction as a subconscious outlet for internal stress, as a result of anxiety and long standing life conflicts (Moulton, 1955). The importance of the patients emotional constitution in relation to masticatory muscle tension was emphasised and directed the gradual paradigm shift towards the significance of psychological factors in TMD aetiology. Masticatory muscle over use producing spasm, pain and fatigue were proposed to establish a vicious cycle of symptom aggrevation and maintenance (Laskin,1969).

Later modifications to the theory suggest a consequence of the psychophysiological disorder leads to limited joint movement and joint sounds (Laskin 1986).
Emotional and experimental stress result in increased masseter muscle activity (Yemm 1979 a,b). EMG recordings did not reveal raised levels of muscle activity in TMD patients compared to controls, but TMD patients showed a more persistent muscle contraction over time suggesting pain may eventually arise due to muscle fatigue. However, these findings were not supported by Moss and Adams 1984.
Rugh and Solberg 1977 also linked emotional stress and episodes of difficult life change with bruxism. Similarly, emotional stress and high force parafunctional activities were proposed to lead to muscle and joint pain, limited movement and joint sounds (Rugh and Solberg,1992) .
The influence of psychological factors on parafunction has since been disputed. However, pain patients demonstrated more anxiety and increased muscle tension at rest. Similarly, when exposed to experimental stress, increased heart rate and systolic blood pressure compared to controls(Carlson et al 1993).

3.5 Personality characteristics and the pain prone patient

In adddition to hypertension and increased heart rate, there are a number of conditions notably chronic pain conditions influenced by psycho physiology,(Feinmann et al,1984a, Katon et al, 1990.)
The relationship between certain personality characteristics and a predisposition to specific somatic disorders was first assumed by (Dunbar 1935).
Rugh and Solberg, 1976 in an extensive literature search did not link TMD to a specific personality trait. Likewise, there was no difference in state and trait anxiety levels in TMD patients and controls, (Marbach 1978). A detailed medical history of

patients with idiopathic facial pain will often reveal that the patient has experienced one or more episodes of chronic pain elsewhere in the body: tension headache, neckacke backacke, irritable bowel pain,pelvic pain, menorrhagia and pruritus (Berry 1969, Gold et al1975, List,2001,John,2003). This highlights the concept of pain vulnerability with different pains occuring at different stages in a patients life (Engel,1959, Feinmann and Harris,1984,) In childhood, ear or abdominal pain, TMD and dysmenorrhia in young adults and pruritus, iritable bowel, neck and backache in later life. Unless recognised as a generalised problem attempts to attribute a differential diagnosis to each pain episode will be unsuccessful and misleading (Feinmann et al,1984, Aghabeigi et al,1992,).

3.6 **Pain and the role of gender**

The high prevalence of TMD amongst females is supported by studies of various design,(LeResche,199 (LeReche,2001)7, Epker,1999, Rauhala,2000, Macfarlane, 2002, Huang,2002, Rantale,2003). One explanation to account for the higher female predominance in the TMD clinic population is that females seek health care more readily than males (LeResche,2001). However, hormonal influence in the possible pathological mechanism of TMD has also been suggested,(LeResche1997, MacFarlane,2002). It has been suggested oestrogen receptors in the TMJ may induce pathology due to hormonal activation of the cytokine production pathway, (Gollehon, 2001, Phillips,2001).Other patho-mechanisms suggest males and females may not process pain signals in the same manner with different perception and reaction to pain,(Bradburg,2003). Lavelle,2002, suggests intensity of pain relates to need for treatment rather than severity of the pathological process and females with high levels

of anxiety were found less receptive to treament with less reduction in pain compared to males,(Rollman,2003).

3.7 Emotional life stress, vulnerablity and coping ability

Chronic pain may arise in response to life stress. Acute stress in the form of an adverse life event such as a bereavement or trauma or on going stress including: chronic illness in the family or family conflict; social isolation; marital, employment or financial difficulties and in children schooling problems, parental strife or divorce. In contrast positive life events such as promotion, marriage or moving house may also be psychological stressors related to pain onset. Inadequate and unstable parental support in children appears to be life long predisposing factors in vulnerable individuals which can lead to chronic somatisation, (Feinmann and Harris 1984, Speculand 1984).
Acute and chronic social stress can have a synergistic effect, in comorbid anxiety, pain and depression,(Campbell,2003). Higher levels of stressful life events have been reported in idiopathic facial pain patients.(Aghabeigi et al,1992).
Schnurr et al,1990, suggest TMD patients do not appear to be significantly different from other pain patients or healthy controls in personality type, response to illness, attitudes towards healthcare or ways of coping with stress.
Marbach et al. 1992 and Southwell et al. 1990, did not establish a difference between TMD patients and controls with regard to adverse life events. However, patients had fewer sources of emotional support and hence found difficulty coping. The overall effect on the individual depends on the ability to adapt to stress. Adaptation or 'coping' ability is now a significant area of research activity on stress and chronic pain, (Keefe1992, Lazarus,1993). Poor psychosocial adjustment is one of the factors associated with failure of long-term treatment in orofacial pain,(Feinmannm1993). The

direction of the pain-depression relationship in TMD has not been established,(Rollman,2000).It is however considered that long-term pain in general leads to depression rather than vice versa (Campbell,2003, Marbach,1999).

The analogy between stress, pain and chronic illness remains unclear.To explain the nature of the painful peripheral experience in relation to a central psychological disturbance it is necessary to investigate central biological markers.

3.8 Biochemistry- correlating pain with signs of depression

3.8.1 State markers

A number of biological abnormalities have been shown to represent current state markers of chronic pain and endogenous depression. These include: hypercortisolaemia, abnormal dexamethasone suppression test, low concentration of serum and urine melatonin levels, low CSF 5-hydroxyindolaceitic acid , low platelet monoamine oxidase activity and low palatelet 3H- imipramine binding, (Tominagen, 1999,Campbell,2003).Bradykinin may also be implicated in the pathogenesis of TMD,(Suzuki,2003).

3.8.2 Trait markers

Impaired conjugation of tyramine sulphate, analysed in urine, is a trait or constant marker of endogenous depression and chronic facial pain although the basis for the defect is not clear.(Aghabeigi,1993)

Such findings provide further support for the theory that a common biological pathogenesis may subserve both depression and chronic pain, (Aghabeighi, 1983).

McGregor 2003, suggests elevated urinary levels of amino acids might be related to hyperalgesia.

3.8.3 Correlating pain with biochemical signs of inflammation

Aleksandovskii 1988, demonstrated increased free radical generation associated with stress and pain in animals. Facial pain patients reveal evidence of increased oxygen free radical activity in their plasma and synovial fluid (Wasil, 1990). Nevertheless, there is no significant differences between painful and symptom free sides of the TMJ (Aghabeigi,1990)

The TMJ capsule was found to contain neuropeptide rich nerve endings and neuropeptides in painful joints (Holmlund et al, 1991)

Analysis of synovial fluid reveals abnormal concentration of plasma proteins or neurotransmitters (Israel,1989, Kopp et al,1983, Quinn and Bezan,1990, Appelgren et al 1993). In addition, degradation of enzymes, metabolic by products, pain transmitters, inflammation and degeneration in the TMJ were observed.

Aghabeighi,1990, meanwhile demonstrated 15 HETE, a metabolite of the hyperalgesic eicosanoid 15 HPETE, in the synovial fluid. Sakamaki, 2001, suggests plasminogen activator, plasmin and kalikrein macromolecules may be involved in the pathogenesis of synovitis and resorption of the TMJ.

Alterations in synovial fluid lubrication and viscosity may initiate clicking and internal derangement of the TMJ ,(Toller,1961).The friction on the disc may cause impaired movement and adhesion, due to free radical induced damage to the fibrocartilage.

Harris, 1995, proposed that the series of biochemical events in TMD involve release of substance P and CGRP which cause vasodilatation and inflammation generating free radicals from leucocytes.The localised free radicals damage the cell membranes to produce algaesic eicosanoids: PGF2 and 15 HPETE. The combination of 15 HPETE and substance P produces chronic pain not inhibited by the NSAID's (Nakarmura-Craig and Smith,1988)

In summary emotional distress in association with local physical stress in a biochemically and psychologically vulnerable subject promotes release of neuropeptides in the target tissue joint capsule or muscles producing synovitis, capsulitis and or myofascial pain (Harris,1990)

3.9 The biopsychosocial approach to TMD

The psychological factors not the occlusion has finally begun to cause a paradigm shift in the underlying management of TMD, (Marbach and Raphael,1999).
Molin, 1999, succintly describes how the focus of attention must shift from "bite to mind". Psychological factors clearly appear to play a critical role in TMD yet the quest for the underlying psychopathology and physical pathological processes continues. Adopting the 'biopsychosocial model of pain', is essential in order to understand more fully the relationship between the pathogenesis of chronic pain and psychosocial factors,(Ong,2003). Diagnosis and management based on physical and psychological axes allows both these aspects to be analysed and provides an hollistic approach to patient care. If treatment does not embrace the interaction of biomedical and psychosocial factors, therapeutic outcome may be favourable but only temporary, (Hampf,1993, Sherman, 2001).Therefore, appropriate and accountable treatment can only be provided when adhering to the biopsychosocial model,(Goldstein,1999).

3.10 Risk factors and chronicity in TMD

The biopsychosocial model has also been used to identify psychosocial factors prediciting the development of chronicity amongst acute TMD cases, indicating a positive correlation with muscular groups. (Epker,1999).

Recently, risk factors for myofascial pain and arthralgia were identified to be trauma, parafunctional habits, third molar surgery, somatization and female gender, (Huang, 2002, Conti, 2003).Rantala,2003, related pathogenesis to work, social and psychological factors. The psychological factors appear to play a more prominent role when pain is of a muscular basis, (Auerbach, 2001,Yap,2002). Individuals with masticatory muscle pain tend to report greater levels of depression and anxiety than matched controls, (Carlson,1998).

The conversion from acute to long term chronic pain may result from the body's inability to restore normal physiological function (Loeser,1999). The onset, perpetuation and exacerbation of chronic pain may in turn be influenced by psychosocial factors,(Neligh,1996,Fricton,1996).Those patients who develop chronic TMD do appear to have more psychosocial distress prior to developing chronicity than those whose acute symptoms subside,(Phillips,2001).Early intervention with clear explanation and discussion of the condition with support in addressing psychosocial issues may therefore aid in preventing the development of chronicity. (Epker,1999).

CHAPTER IV

TEMPOROMANDIBULAR DISORDERS

MANAGEMENT

CHAPTER IV

4.0 MANAGEMENT

4.1 Aims

The primary aim of management is similar in many respects to treating other rheumatic or orthopaedic disorders (McNeil, 1993). To relieve or decrease pain and suffering, to decrease adverse loading, to restore function and to restore normal daily activities of talking, eating and yawning.

In the majority of cases treatment is focused on prevention and cure although palliative forms of care may be required in the more unyielding cases. Choice of treatment is to some extent dependent on the nature of the contributing aetiological factors. This should be gleaned from a detailed history although not always clearly identifiable due to the complex combination of factors. Presentation of the condition may be in acute or chronic form, transient and self-limiting or constant and unremitting.

The decision is which patients require treatment, when, how and with what choice of treatment?

Treatment can broadly be divided into:-

- Conservative
- Psychological
- Physical
- Medical
- Surgical

The first line of action is of course conservative, with a clear explanation of the condition, informed reassurance and advice on management. Patients can only be active and informed partners in managing their own disease if given comprehensive information (Tattershall 1989). Mayberry,1996, emphasises a simple handout is

invaluable for communication and reassurance. Self-management was reported to help 60 to 90% of patients with TMD, (Wright and Schiffman, 1995). The effect of reassurance undoubtedly reflects the high placebo response associated with reduced anxiety, the strength of the doctor-patient relationship and the expectations of the patient and the clinician.

When choosing further treatment a vast array of options exist many of which have unproven benefit. A schism is said to exist between the researcher and clinician into treatment decisions for the TMJ patient (Von Korff, 1988, Bader and Sturgers, 1995). The failure to practice evidence based medicine and to incorporate the principles derived from clinical epidemiology, is believed to lie at the source of this problem, (Raphael and Marbach, 1997).

4.2 Evidence based medicine (EBM)

The traditional treatment paradigm has relied upon: clinical training, basic principles of pathophysiology, textbooks, subsequent experience and clinical observation to evaluate effectiveness of treatments The resultant problems arising have included: -

1) Heterogeneity in treatment practice, depending on site of referral, patients with virtually identical signs and symptoms of TMD receive drastically different treatment.

2) Unpredictability of outcome (Clark, 1988)

3) Adverse effects of treatment.

4) Cost due to several treatments

The difference between EBM and the traditional treatment paradigm resides in the source upon which clinicians rely to base treatment. Evidence based medicine does not reject clinical training and experience but augments this with a critical synthesis of

research evidence, to update knowledge by active and critical evaluation (Mohl and Ohrbach, 1992).

Following a traditional treatment paradigm three outcomes are possible; the patient improves, the patient does not improve or the patient does not return for follow-up and treatment remains unknown. The factors that lead to incorrect conclusions of treatment efficacy when relying on clinical observation alone, may therefore include:

1) Placebo effect of treatment

2) Statistical regression towards the mean

3) Spontaneous remission

4) Natural variability of signs and symptoms

5) Failure to consider treatment drop out

6) Bias in self-reporting of symptom remission

(Marbach and Raphael, 1997)

The strength of inference on effectiveness of treatment must therefore shift to the well designed studies preferably double blind randomised controlled clinical trials. The National Institute of Health Technology Assessment on the management of TMD Disorders held in Bethesda, Maryland in 1996, concluded that "... Data does not support the superiority of any method for initial management of most TMD problems....Efficacy of most treatment is unknown because they have not been evaluated adequately in long term studies or virtually none in randomised controlled trials (RCT's) Most patients experience improvement or relief of symptoms with conservative treatment and patients should receive initial management using non invasive and reversible therapy. In a small percentage of patients surgical intervention may be considered where significant

and persistent pain, dysfunction and internal derangement of the TMJ exist. Cognitive behavioural therapies were felt to be effective approaches in managing chronic pain." Marbach and Raphael, 1997, explains "when the scientifically accepted knowledge of treatment efficacy is poor, safety becomes a primary consideration. The safest treatments are non invasive and reversible."

The treatment of TMD will now be reviewed from an evidence based medicine approach with emphasis on examining the medical and physical therapies to be used in the RCT.

4.3 Conservative management

All patients should receive counselling, education and informed reassurance at their initial consultation, reinforced at future appointments. The most important aspect of therapy is a warm, positive and reassuring attitude on behalf of the clinician,(Griffiths, 1987).As the first line of treatment, a clear explanation of the condition, informed reassurance, advice on management and a simple handout, has been reported to help 40 – 60 % of patients, without the need for further intervention (Wright and Schiffman, 1995).

4.4 PSYCHOLOGICAL THERAPIES

4.4.1 Simple behavioural modification

Conservative management and the interaction between clinician and patient, is the simplest form of psychological therapy. Modification of maladaptive habits can often be achieved by the patient when informed at the initial consultation. Awareness of raised stress levels can result in the patient incorporating simple relaxation strategies into daily life. Abnormal jaw posturing, clenching or chewing habits, during the day when under stress, can be modified by self monitoring procedures. Persistent habits

may require reinforcement of advice or a short structured programme by clinicians trained in behavioural modification (Rugh, 1987).

The effectiveness of a short skills training programme in physical self-regulation, controlled breathing, postural relaxation and proprioceptive re-education proved effective in short and long-term management of muscular facial pain in a randomised controlled trial, (Carlson et al,2001). Habit reversal therapy in TMD, with control groups, again revealed pain reduction, accompanied by reduction in oral habits with minimal clinical contact but therapeutic self-reliance, (Townsen, 2001).

Significant, adverse contributing factors may result in refractory pain which requires more significant behavioural modification. A more structured approach to management is required with progressive relaxation therapy, counselling and cognitive restructuring provided by a clinical psychologist.

4.4.2 Cognitive behavioural therapies

Cognitive behavioural therapy (CBT), divided into cognitive restructuring and behavioural coping skills has proven beneficial to patients suffering from chronic pain, (Turner, 2001).

In simplified terms; cognitive therapy allows patients to examine thought patterns and how they can distort and influence quality of life; whilst behavioural therapy is used to alter responses and habitual reactions to situations by developing relaxation and coping skills. Interventions in CBT include: setting goals, challenging negative thoughts, relaxation and breathing skills, visualization exercises, developing coping strategies, assertiveness and stress management, (Morley,1999). Turk (1994) describes the inter related components of treatment to include: education, skills acquisition, cognitive and behavioural rehearsal, homework, generalization and maintenance.

CBT has been found effective in reducing pain and disability in TMD, particularly in combination with other treatment modalities including medication, (Harrison et al,1997) and biofeedback (Gardea et al, 2001).

Dworkin, 1994, found TMD patients suffering from dysfunctional profiles, coupled to high distress and pain, did not benefit from brief CBT alone. The need for more research in the application of CBT in TMD was emphasised (Turner, 1995).

Dworkin et al, 2002, conducted a randomised controlled trial to examine the intervention of six sessions of CBT. He concluded that patients with psychosocial disability in relation to TMD showed improvement in pain variables and this may suggest dysfunctional patients respond well to a more comprehensive trial of CBT.

It is interesting to note that individuals who suffer from dysfunctional profiles or patterns of TMD, notably high distress and pain were associated with both failure of conservative and surgical therapy, (Dahlstrom, 1997). Patients who are conscientiously supported and appropriately referred for specialist care, do not seek help through litigation. The converse is unfortunately true in the situation of prolonged and unsuccessful physical and surgical therapy, (Harris et al, 1993). In a tertiary referral centre patients have frequently received numerous unsuccessful therapies and are therefore more likely to exhibit dysfunctional behaviour. CBT is frequently required as adjunctive therapy and severely dysfunctional patients or those suffering from anxiety, depression or with a history of concomitant psychiatric illness may require direct referral to a liaison Psychiatrist or Psychiatric team.

4.5 PHYSICAL THERAPIES

These include: posture training, simple mechanical exercise and mobilization; thermal application of hot and cold; biofeedback techniques using EMG to monitor muscle activity; TENs to achieve temporary relief of chronic localized joint and muscle pain; US, short wave diathermy, iontophoresis; injections; acupuncture and occlusal splint therapy.

4.5.1 Posture training

Posture training is focused on preventing unnecessary increased muscle contraction and aims to maintain a relaxed orthostatic posture, preventing protrusion of the mandible and increased head, neck, shoulder, masticatory and tongue muscle activity.

The head assumes greater effective weight the more anterior it is positioned in relation to the spinal cord. At rest the teeth should be a few millimetres apart, the mandible relaxed and the tongue resting in the floor of the mouth, the anterior portion resting against the anterior palate.

The benefits of posture training in TMD were recognised as an area for further investigation (Darlow et al, 1987).A training programme of physical self-regulation: breathing, postural relaxation and proprioceptive re-education has been found beneficial in short and longterm management of myofacial pain,(Carlson,2001).

4.5.2 Thermal application

Heat and cold applied to the skin, block pain in the underlying masticatory muscles and TMJ for a short time span of around 20 minutes. This can help muscle relaxation of previously sore, tense muscles, reducing spindle response and enabling the start of effective physical exercises to restore function, (Lehmann, 1999).

The application of superficial heat in its simplest form includes a hot compress, warm towel, covered hot water bottle or infra- red waves for (10-20 minutes). However heat is contraindicated in cases of acute inflammation and infection.

Ethyl chloride spray, a vapour-coolant applied to the surface of the skin over masticatory muscles, followed by the individual actively stretching muscles is termed the spay-stretch technique. Skin should not become frosted and the eyes, ears and nasal mucosa should be protected during application. Benefit is thought to be gained by inactivation of myofacial trigger points. (Travell et al,1983, Jaeger and Reeves, 1986).

4.5.3 **Mechanical exercises**

Jaw exercise is important in maintaining normal comfort, function and stability of the TMJ and associated musculature.

Exercise aims to improve mobility of the jaw, strengthen and enhance coordination of muscles and to eliminate habitual and damaging jaw movement and posturing (Au and Klineberg, 1993, Clark et al 1990, Carlson et al, 1991).

Three types of generally recognised exercises include:

- Repetitive, to achieve coordinated, rhythmic muscle activity.
- Isotonic, to increase range of motion.
- Isometric, to increase muscle strength.

Opening/closing, protrusion/retrusion and lateral excursion are the principle movements.

Exercises can be staged from small to maximal movement and then against resistance provided by the hands to increase strength. Contraction of agonist muscles results in relaxation of antagonists. Initially adjunctive therapy, such as thermal application to relax hyperactive masticatory muscles may be necessary prior to exercising.

Encouragement to exercise the jaw is advised, particularly in the light of recent evidence that suggests TMD patients exhibit a reluctance to exercise the jaw for fear of re injury, (Newton-John et al, 2005).

Contraindications to physical exercises include unhealed fractures, acute arthritis and acute infection in the facial region.

4.5.4 **Biofeedback and EMG** (Electromyography feedback)

Biofeedback mechanisms can be utilized in relaxation therapy. The equipment consists of: a pair of surface electrodes, a millivoltmeter with amplifier, visual and auditory display to allow the patient to observe the physiological response of muscle contraction and relaxation. Muscle tension of the masticatory muscles whilst clenching the teeth can be observed and the individual taught to relax the muscles accordingly. Controlled studies reveal a decrease in muscle activity and nocturnal bruxism but the benefit is only short-term, (Pierce and Gale, 1988, Erlandson and Poppen, 1989).

4.5.5 **'Mind-body' therapies**

Yoga, relaxation, meditation, imagery, hypnosis and biofeedback are considered 'mind-body' therapies (Astin, 2004). Schaelaekens, 2003, reports the anxiety and pain complex may be the most common indication for hypnosis in the dental setting. The aim of relaxation is to decrease sympathetically mediated metabolic activity (Jessup1994). A state of relaxation achieved by techniques which relieve individual stress levels may be beneficial in conditions where stress is an important factor in the genesis and maintenance of pain such as musculoskeletal disorders, (Gura,2002). Hypnotic induced reduction in duration, frequency and intensity of TMD pain has been observed, (Siomon, 2000, Winocur,2002). Further RCT are required.

4.5.6 **Ultra sound** (US), short wave diathermy

This mode of treatment involves deep heat transmission through tissue, up to a depth of 5cm. Heat energy is converted from high frequency oscillation of the transducer head, (Ziskin et al, 1990)

The temporary analgesic and muscle relaxation effect is supposedly a combination of mechanical vibration and thermal energy. Deep tissues may increase in temperature up to 45°C, increasing elasticity and plasticity of collagen, a useful adjunct prior to exercise.

Musculoskeletal chronic pain of the joints, extra capsular soft tissues, muscle contraction and tendonitis has been reportedly treated by US in the literature but there are no RCT for TMD (Esposito et al, 1984, Talatter et al, 1986).

Further research is required to determine optimal frequency, intensity and duration of treatment including number and exposure length of sessions, (Mohl et al, 1990, Hashish et al, 1986).

US should be avoided during TMJ growth or in patients with pacemakers. Metal objects such as earrings and necklaces should be removed from the area to be treated.

4.5.7 **Phonophoresis and Iontophoresis**

Phonophoresis uses US to carry medication into tissues, whilst Iontophoresis uses an electrical gradient to drive an ionic form of medication, usually corticosteroids, into the tissue. (Lark and Gangaros, 1990, Schiffman and Braun, 1993). The efficacy of the former is unknown and the latter requires further evidence (Wise, 1982, Reid et al, 1994). A RCT of iontophoretic delivery of dexamthasone and lidocaine improved mandibular function but did not reduce pain,(Schiffman et al,1996)

4.5.8 **Injections**

Local anaesthetic injections into myofascial trigger points have been used in the management of myofacial pain alone and in combination with muscle stretching and mobilization (Jaeger and Skootsky, 1987, Phero et al, 1987). Lignocaine (Procaine) 1-2% without adrenaline (epinephrine) and diluted to 0.5% with sterile saline is recommended for trigger point injections because of low myotoxicity (Ritchie and Greene, 1985).

Interruption of muscle pain cycles may result in pain relief beyond the duration of the anaesthetic. It is recommended that myoneural block therapy should not be used as initial or sole therapy but only as an adjunct to other physical therapy, pharmacotherpy and behavioural techniques, (Phero et al, 1987).

4.5.9 **Acupuncture**

The mechanism of action, for acupuncture, is not fully understood but is believed to rely on neural and humoural pathways (Rosted, 1998). Wong, 2003 in a case series suggested combined therapy of acupuncture with occlusal splint and point injections to be useful in managing TMD. Acupuncture alone, in several randomised controlled studies has been shown comparable to more conventional therapy but generally less acceptable to patients due to the use of needles (Raustia et al, 1985, Johansson et al, 1991, List et al, 1993, Myers, 2002).The level of analgesia induced by this method may therefore be modified by stress and anxiety (Wilderstrom-Noga, 1998).

4.5.10 **Electrotherapy**

Electrotherapy includes TENs (Transcutaneous electrical nerve stimulation), EGS (Electrogalvanic stimulation) and microvoltage stimulation which may produce

thermal, histochemical and physiological changes in the muscles and joints.

TENs is used primarily for temporary relief of chronic localized joint and muscle pain using low voltage, low amperage, biphasic current of varied frequency causing low threshold sensory stimulation to block pain impulses (Dubner, 1978, Moystad et al,1990).The electrical stimulation of acupuncture needles in comparison to TENs has not shown a significant difference if applied in the same dermatome,(Butler,2001).In a recent study no substantial improvement of TMD signs and symptoms was managed with TENs,(Alvarez-Arenal,2002).

EGS uses high-voltage, low amperage, monophasic current of varied frequency (Binder,1981).Micro current electrical stimulation is designed to produce a microvoltage similar to that which occurs at the synaptic junction. Payne, 1994, revealed no significant results in patients treated with EGS compared to a control group.

Both TENs and EGC may decrease muscle pain and hyperactivity and aid in muscle re-education but clinical evidence for electrotherapy usage in TMD remains lacking.

4.6 OCCLUSAL APPLIANCES

Variable terminology for the same appliance includes: Interocclusal splints, intraoral appliances, bite guards, bite planes, night guards, orthopaedic appliances, orthotics and orthoses. The item can be defined as any removable appliance used to relieve the symptoms of TMJ and associated muscular pain and dysfunction. They are normally constructed of acrylic resin with occasional wire attachments for retention.

4.6.1 **Historical perspective**

Historically, the purpose of occlusal appliances has been to treat a variety of symptoms which can be related to three specific sites: TMJ, associated musculature and teeth.

1) **TMJ** -Relieve pain and dysfunction

-Alteration of joint loading and stabilization

-Alter structural alignment of condyles and discs

2) **Muscles** - Relaxation of painful and/or dysfunctional masticatory musculature.

- Decrease abnormal muscle activity to:- -Improve neuromuscular coordination

-Reduce aberrant and parafunctional habits

(clenching and bruxism)

3) **Teeth** - Stabilize the occlusion in static and dynamic relationship.

- Eliminate occlusal interferences

- Redistribute force to prevent adverse occlusal loading

- Protect teeth from excessive wear and mobility

The main aim of treatment is to relieve pain. However, clicking may be present with or without pain and is a result of uncoordinated movement of the condylar head and TMJ disc. Reducible anterior disc displacement is the clicking condition which splint therapy most frequently attempts to treat and is discussed later in the review.

With regard to the musculoskeletal pain and dysfunction the three main categories for treatment are myalgia (muscle pain), limitation in mouth opening and mandibular incoordination.Appliance design varies according to specific or multiple aims of therapy.To explain how occlusal appliances are believed to function it is necessary to examine the five distinct theories as reviewed by Clark, 1984 and Colt, 1991.

4.6.2 **Theories**

4.6.2.1 **Occlusal disengagement theory.**

This theory advocates the patient is given an "interference free, ideal occlusal scheme" to decrease or prevent abnormal muscle activity so providing stability to the TMJ's, (Ramfjord and Ash, 1971, Posselt, 1968). The splint is designed with simultaneous, bilateral, occlusal contact of all teeth in centric relation with canine and/or anterior tooth guidance in excursive movements. The anterior bite plane or more commonly the full maxillary stabilization appliance, fulfils this role.

Dawson ,1989, clearly explains the basic function of splints is to prevent the existing occlusion from controlling jaw relationship in maximum intercuspation. When partially or completely covered the splint material in effect becomes the new occluding surface. The mandible and hence condylar axis is dictated by the new ideal occlusion established by the splint. Secondary to the disengagement of the occlusion and control of jaw relationship, the splint will help distribute occlusal force, reduce tooth wear and stabilize unexposed and weak teeth.

4.6.2.2 **Occlusal vertical dimension (OVD) theory**

Costen ,1934 and Goodfriend ,1933, first suggested OVD theory, which was further elaborated by Block, 1947 and Christensen, 1970. Based on restoring previously lost OVD it was aimed to reduce or eliminate aberrant muscle activity which had arisen due to an abnormal vertical dimension.

Re-establishing "original" OVD however proves difficult. Dawson ,1989, points out that occlusal appliances always involve some increase in OVD but the change in OVD does not affect the position of the condylar axis in centric relation. Condylar rotation stays on a fixed axis in centric relations for 15mm or more of opening before forward

translation. Up to the point of translation, changes in the vertical axis do not effect the position of condylar axis.

4.6.2.3 **Maxillomandibular realignment theory**

This was suggested by Lerman, 1974, Lieb, 1977 and Jankelson, 1979. The mandible is thought to assume an abnormal unbalanced position relative to the maxilla in maximum intercusspation (ICP). Altering this relationship to a more physiologically and anatomically correct jaw position it is theorized dysfunctional musculoskeletal symptoms can be improved or eliminated by achieving "neuromuscular balance".

At present there are three ways to determine the need for mandibular realignment.

Firstly, Dawson, 1974, describes a "ligamentous determined jaw position" or centric relation position. Obtaining this position involves clinical jaw manipulation in a hinge type movement whilst maintaining upward and backward pressure to ensure seating the condyles in the TMJ fossae.

Secondly, Lieb ,1977, describes identification and marking of anatomical land marks on maxillary and mandibular dental casts. These are used to align and reorientate the models for construction of a splint. Skeletal and dental asymmetries and irregularities occur in a significant proportion of the population and there have also been no objective studies examining the efficacy of such a radical approach.

The third approach is a muscle-determined positioning of the mandible found by two techniques. Jankelson, 1979, used a TENS transcutaneous electrical stimulation of low frequency applied to the preauricular area to stimulate the trigeminal nerve. It is postulated motor nerve excitation of the trigeminal, produces a jaw closing trajectory resulting in a neuronmuscularly balanced jaw position. This is recorded and a splint constructed. Intercuspal position is usually anterior on such appliances causing

alteration to the occlusal relationship, again clinical studies have not been undertaken. The second technique uses a fluid-filled bag that theoretically dictates neuromuscular realignment of the mandible ignoring the position dictated by teeth, Lerman,1974. There has been no reported clinical testing of this appliance.

4.6.2 4. **Temporomandibular joint repositioning theory**

This was proposed by Farrar, 1972, Gaush and Kilmer, 1977, Weinberg, 1979, Thompson, 1954, Witzig and Spahl, 1987. The concept is to correct the position of the condyle in the fossa and so improve the function of the TMJ. The position of the condyle is usually determined radiographically but there may be errors in joint position measurements, especially with flat plane transcranial views. Variations in condylar position also exist in an asymptomatic population, (Pullinger et al, 1985).
Another theory attempts to locate the condyle in a specific therapeutic position in the fossa, to treat specific intracapuslar derangement, (Gaush and Kulmer, 1977). By placing the mandible in a new position, change in disc condyle relationship is hopefully achieved. Holding the mandible in a forward position is thought to allow healing of retrodiscal tissue. A repositioning splint is used for this purpose. If disc repositioning occurs and there is resolution of the click then the mandible can be moved sequentially to the pre-treatment normal anatomical position by repeated splint adjustments. Hopefully clicking will not reoccur. In some cases irreversible alterations of the occlusion have been undertaken to allow permanent reposition of the mandible anteriorly. The resolution of one problem may produce more serious occlusal problems. Short term relief of a click may cause long term dysfunctional condylar remodelling and expense due to problems in occlusal stabilization.

4.6.2.5 **Cognitive awareness theory.**

This was proposed by Greene and Laskin,1972, Rugh and Robins, 1981. This relies on the concept that any intra oral appliance in the mouth is a constant reminder for the patient to alter behaviour regarding the jaw position, tooth contact and abnormal muscle activity. This increased awareness of jaw position, change in oral tactile stimuli and decreased oral volume caused by the splint can help in altering or reducing harmful behaviour such as parafunctional activity. This theory would of course therefore apply to any design of splint.

4.6.2.6 **An overview of splint therapy**

Appliances to cover the occlusal surface of teeth to cause an effect on the jaw joint were first described over 120 years ago by Kingsley, 1877.Although materials have improved and new theories on function proposed, the basic aims of treatment and design have changed little. A definitive mechanism or theory of splint action remains elusive. However, new imaging techniques, an awareness of psycho- physiological interaction and the promotion of good scientific clinical research brings us nearer to a clearer understanding of what constitutes the most appropriate form of therapy for patients suffering from Facial Arthromyalgia(Temporomandibular joint dysfunction). At present clinicians must be content to follow the recommendations of non-invasive and reversible therapy in the initial management of the disorder as proposed by the National Institute of Health Technology (1996).Not all occlusal appliances can be regarded as providing an irreversible form of therapy. Functional and morphologic changes in the occlusion following long-term use of certain appliances can occur. With any appliance, complications of psychological dependence can occur and poor oral hygiene of the appliance and teeth can cause caries or periodontal problems.

Currently, the full coverage stabilization appliance offers reversible therapy with no permanent occlusal alteration. It has therefore been scrutinized more thoroughly than other appliances in the review to access potential clinical efficacy.

4.6.3 Appliance design

Occlusal appliances are designed to be directive (predetermined occlusal position) or permissive (no predetermined occlusal position), constructed from resilient or hard materials and to provide either full or partial coverage of the occlusion.

4.6.4 Partial coverage occlusal appliance

Some but not all opposing teeth are in contact with the appliance. Anterior or posterior teeth are covered in the maxillary or mandibular arch.

Table 3a: Partial coverage appliances

Anterior partial coverage appliances	Posterior partial coverage appliances
• Anterior bite plane/plate - Hawley Appliance - Sved Appliance - Immediate plate	• Posterior bite plane/plate/onlay
	• Posterior occlusal pivots
• Anterior jig - Lucia jig	• Repositioning appliance - MORA (Mandibular orthopaedic repositioning appliance)

4.6.4.1 Anterior partial coverage appliances

4.6.4.1.1 Anterior Bite Plane.

This is generally a rigid construction for the maxilla with a contact surface provided for mandibular anterior teeth only with no contact of the posterior teeth. The aims were to disengage the occlusal forces on posterior teeth to allow muscle relaxation

and establish a new occlusal vertical dimension, (Posselt, 1963).

Hawley,1919, published an original article describing a retainer with a biteplane. He designed a palatal coverage appliance with a flat platform behind the maxillary incisors to increase vertical contact between opposing mandibular anterior teeth

A labial arch wire was used to avoid splaying of maxillary anterior teeth. The design could cause trauma to the gingival tissues in the plate and was hence later modified.

Sved,1944, introduced an acrylic appliance which extended a few millimeters over the incisal edge of the maxillary anterior teeth, with once again a palatal plane for contact of opposing mandibular anterior teeth, but also retention clasps on bilateral distal molars. Posselt,1963, recommended the Sved appliance for treatment of TMJ disorders. Ease of fabrication, fitting and adjustment, together with the reported initial effective reduction in symptoms, popularized use.

Both biteplanes are in theory potentially orthodontic appliances which result in tooth movement after prolonged usage. Occlusal forces are altered with a tendency for vertical eruption of the unrestrained posterior teeth, intrusion of anterior teeth and development of an anterior open bite.

The main disadvantages are therefore the potential loss of occlusal stability.

4.6.4.1.2. **Anterior immediate palatal plate.**

Langer,1975, described a short term emergency measure for patients with limited mouth opening and masticatory muscle trismus. The acrylic appliance is fabricated directly into the mouth and seated over the anterior teeth to prevent closure of the mandible into maximum intercusspation.

4.6.4.1.3.**Anterior jig (Lucia Jig)**

Lucia ,1985, designed a jig to obtain multiple centric relation bite registration. The appliance was also suggested to treat some TMJ disorders, (Guinn,1985).The hard acrylic appliance usually covers only the maxillary central incisors with a palatal plane to guide the mandible into centric relation.

The disadvantages of using such an appliance are the need for close supervision since occlusal forces are solely directed to the incisors whilst concern may arise over possible aspiration of the jig due to the small size.

4.6.4.2 **Posterior partial coverage appliances.**

4.6.4.2.1 **Posterior bite plate/plane/onlay appliance.**

Appliances have been made for either the upper or lower arch. The aim was to raise the bite to compensate for the loss of occlusal vertical dimension and hence their use became popular because of the theories of Monson, 1921 and later Lindblom, 1953. Posterior onlays were also considered to relocate the condyle in the middle of the mandibular fossa during jaw closure, (Weinberg, 1979). In simple form the plate consists of two acrylic resin blocks covering premolar and molar teeth joined by a lingual bar, (Lerman, 1974). The plate is popular with patients due to easy speech adaptation and lack of visibility. Unfortunately dentoalveolar changes due to intrusion of posterior teeth, extrusion of anterior teeth and resultant lateral posterior open bite may develop, with full time wear as demonstrated in animal experiments, (Ramfjord and Blankenship,1987). Such unwanted occlusal changes are the major disadvantage. However, it is interesting to note that deliberate axial movement has been used

increasingly as a modality to create space for restorative procedures where the teeth are worn,(Dallet et al, 1975 , Ibbetson and Setchell, 1989).

4.6.4.2.2.**Posterior occlusal pivots.**

This method involves single, bilateral premolar or molar tooth contact in order to disengage the dentition and relieve mechanical loading on the TMJ. Niemann ,1984, describes pivots as a diagnostic aid in TMJ dysfunction whilst the pivot appliance treatment is described by Sears, 1956. It was proposed that pivots provided jaw rest and relaxation with establishment of a new occluso-vertical dimension.

Clinically, composite or acrylic ridges can be applied to the chosen bilateral tooth region on a mandibular or maxillary onlay appliance. Alternatively, material is bonded directly to the teeth or cast metal pivot restorations constructed. Cast or bonded pivots necessitate continual wear which one could imagine to be most uncomfortable for the patient. The particular location of the pivots would tend to affect TMJ loading in relation to altered masticatory muscle vectors. The generation of lateral or vertical occlusal forces on teeth are however unpredictable. Contact with opposing teeth may simply increase vertical dimension or position the mandible protrusively or retrusively. There is potential for tooth mobility and intrusion but significant distraction or unloading of the TMJ's is thought unlikely without external chin retraction, (Louis, 1990).Pivots in general are therefore not recommended due to discomfort in use and irreversible tooth movement, (Ramjford and Ash,1986).

4.6.4.2.3 **Mandibular orthopaedic repositioning appliance. (MORA)**

The mandibular orthopaedic repositioning appliance (MORA) or Gelb splint was popularly used in the 1970's and described by Lieb,1977.

It is a hard, acrylic, mandibular, posterior, coverage splint with a lingual connecting bar and occlusal indentations to position the mandible protrusively. Despite comfort and relief of pain, appliances may lead to severe occlusal alteration even after 1-2 weeks,(Ash ,1984).

The malocclusion which develops is often more severe than that experienced with full coverage repositioning appliances. Vlachos,1995, explains that since MORA's cover posterior teeth only, dentoalveolar changes of posterior teeth intrusion and eruption of anterior teeth may compound the occlusal alterations which occur as a result of the newly repositioned condyles. The extent of posterior open bite which develops is therefore dependent on the amount of anterior positioning in relation to the path of altered condylar movement and with respect to the initial, anterior teeth, open bite and over jet.

To reposition teeth post therapy often requires extensive orthodontic, restorative, prosthetic or even surgical procedures, (Haden, 1982).

Occlusal corrections can involve unsuccessful attempts to extrude the posterior teeth using a Sved appliance with posterior stepping of the mandible into an intercuspal position. Even if tooth movement is achieved, relapse of the posterior open bite and return of symptoms may develop within a few months, (Ash, 1986).

Maloney and Howard,1986, in a long-term study also suggest symptoms tend to reappear and report usage is based on anecdotal evidence with a lack of scientific data. Warnings against the use of MORA appliances have been issued by (Ash, 1986 and Abbott, 1991).

4.6.5 **Full coverage occlusal appliances**

The maxillary or mandibular dental arch is completely covered. Appliances are either constructed in resilient or hard material and act in either a passive or directive manner.

Table 3b: Full coverage appliances
• **Anterior Repositioning appliance**
• **Resilient Interocclusal appliance**
• **Stabilization appliance**

4.6.5.1 **Anterior Repositioning appliances**

These devices developed following theories of internal derangement of the TMJ expressed by Farrar and McCarty, 1971. The aim was to alter jaw and tooth position in static and functional occlusion and so recapture the anteriorly displaced disc into an ideal position with respect to the condyles, (Clark, 1986). To achieve this, the bite is raised and the mandible is repositioned downwards and forward, beyond any reciprocal click. Correction of the disc-condyle relationship long-term is not necessarily the aim once relief of symptoms is achieved. Kiricos,1987, using MRI imaging questioned the necessity for ideal disc location. Clicking may decrease but it is not usually eliminated. Clicking is usually non progressive and may appear and disappear with or without treatment, (Greene and Laskin, 1988). Long term studies suggest clicking is the symptom most resistant to splint therapy, (Agerberg, 1974).

Designs vary but generally rely on occlusal indentations and guiding planes in hard acrylic to produce altered mandibular position, (Farrar, 1972, Weinberg, 1979). Further adjustment is required during therapy to refine jaw position. Splints may fit the maxilla or mandible and occasionally in the case of LARS (Ligated anterior repositioning splint) are attached to the upper arch. Mandibular appliances have indentations only,

whilst maxillary appliances have guide ramps and indentations and so are more effective in protrusive guidance of the mandible. Since both appliances are full coverage, dentoalveolar changes of tooth extrusion or intrusion should not occur. However, when the jaw is protruded, due to downward movement of the condyles as they translate forward, a space is created between the posterior teeth known as the 'Christensen phenomenon',Huffman and Regonos,1989. As a result of this, repositioning the condyle in a downward, forward position can cause development of irreversible occlusal changes with severe posterior open bite,(Vlachos, 1995).

Hanson et al ,1985, Anderson et al,1985, showed the splint worn full time performed well in short term studies. Clark,1984, reviewing 25 cases suggested suitability of the splint for treatment of disc displacement with reduction.

Moloney and Howard,1986, Okesson ,1988, found in clinical studies that achieving a new occlusion with the disc recaptured was not successful in the long term and it was suggested the stabilizing splint was a more effective alternative.

Greene and Laskin ,1972, disputed the claim that repositioning appliances could replace an anteriorly displaced disc. Lundh and Wetesson ,1989, in their study of 11 cases reported 82% success at 3 years in maintaining position of the disc but raised the issue of treatment cost in relation to symptom severity. They also noted that patients with disc displacement can be successfully treated without permanent repositioning of the condyle due to adaptation of the retrodiscal tissues, a finding previously noted by (Scapiro, 1983).

Originally it was considered that appliances should be worn constantly including meals to establish the new jaw position, (Farrar, 1965). Although initial full time wear is thought to reduce symptoms most rapidly, part time use has now been

advocated to reduce irreversible occlusal change (Okeson, 1993). Nocturnal use only, may reduce joint pain and prevent intermittent disc displacement without reduction on awakening with marked reduction for potential occlusal changes due to limited wear, (Okeson, 1996). Davies and Gray,1987, in their study on the pattern of splint usage found however that 24 hour wear gave the most significant relief of symptoms.
Full time use of the repositioning splint may be effective in decreasing pain and dysfunction but the potentially undesirable occlusal consequences must be considered to avoid the need for extensive restorative and orthodontic treatment. Therefore, when TMJ symptoms resolve, ideally the pre-treatment mandibular position should be re-established. This is achieved by gradually adjusting the appliance to allow posterior jaw relocation (Okeson, 1995). This can be a very time consuming process. On accomplishing the original occlusal relationship, the pain may return possibly due to lack of retrodiscal tissue adaptation. An anterior positioning appliance will again relieve symptoms and more time is then allowed for tissue adaptation before once again attempting to relocate the TMJ. Permanent occlusal therapy in theory should therefore be avoidable, (Okeson, 1995).

4.6.5.2. **Resilient interocclusal appliances.**

Constructed of polyvinyl, these are flexible, soft appliances worn on the maxillary or mandibular dental arch. Straight forward and quick to make, the splint is comfortable and frequently worn as a protective sports bite guard, (Bodenham, 1970). Matthews,1942,Krogh- Poulsen and Olsson,1968, Block et al,1978, have all suggested this simple appliance might be used for patients with a clenching or bruxism habit or symptoms of TMJ pain. Ingersoll and Karens, 1952, Posselt, 1968, noted the appliances are not easily adjusted and have poor durability in use. Okeson ,1987 and Harkens et

al, 1988, reported mixed results whilst Singh and Berry, 1985, report concern over the effects on occlusal contacts. Wright et al ,1995, in a short term study of soft splints suggest efficacy relates to dental appliance stability and that occlusal changes do not occur when stable interdental contacts already exist. If a positive improvement does occur with these appliances it may in fact be related to a cognitive awareness in perhaps altering patients teeth clenching or abnormal muscle behavioural patterns.
Short term treatment in adults appears to be useful in reducing masticatory muscle pain, (Pettergill et al, 1998). Short term treatment of children with mixed dentition seem most appropriate as the appliance is reported to have minimal effect on dental development, (Wright et al, 1995).

4.6.5.3.**Stabilization appliances**(Flat plane, gnathologic, muscle relaxation splints)
These provide essentially reversible therapy for facial arthromyalgia since there should be no permanent occlusal changes. The benefits of this design are to resist alterations in tooth and jaw position whilst providing stable contacts to engage all opposing teeth. Nelson,1995, explains that in order to achieve this, the material for construction should be thermally and dimensionally stable, although convenient to use and should resist occlusal forces generated by the patient. Coverage of one arch should provide non-traumatic occlusal contact for all opposing teeth without dictating a mandibular position on closure. Jaw position on closure is generally just anterior to an unstrained centric relation but initial guidance into retruded axis position may be required if muscle splinting is significant, (Clark, 1988).
Splints have been designed for the mandibular arch such as the Tanner Appliance or the Maxillary Arch the most popular type being the Michigan splint.
Although a mandibular appliance has the advantage of being less visible and

allowing easier adaptation in speech if worn during the day, establishing vertical occlusal contact may be awkward with the maxillary anterior teeth. Nelson,1995, indicates class III or posterior buccal cross bite relations may be the exceptions in favouring a mandibular design. Maxillary appliances however allow vertical occlusal contact with the mandibular incisors for the majority of overjet, over bite incisor relations. It is also easier to incorporate anterior and lateral canine guidance in a maxillary appliance particularly where there is marked overjet. Maxillary appliances generally offer superior stability to mandibular appliances noted by Clark,1988. Despite a number of variations in design, the one most widely advocated is the modification of the Michigan splint emphasizing canine guidance as described by (Ramjford ,1966).

This is a heat cured acrylic, clear appliance. Heat cured polymethyl methacrylate is considered the most suitable material, (Steele et al, 1992). Ramjford and Ash, 1985, indicate that the splint should be adjusted so that all opposing teeth achieve simultaneous, stable, occlusal contacts. They also specify there should be no occlusal interferences and preferably no incisal guidance with a mild gradual cuspid rise incorporated starting 0.5mm from centric occlusion and sufficiently steep to separate posterior teeth during lateral and protrusive excursive jaw movements so avoiding non working side interferences.

McNeill,1993, explains the appliance is designed to protect teeth, decrease bruxism, relax musculature and redistribute forces. Tsuga et al ,1989, found a positive effect on TMJ symptoms and short term effectiveness of the appliance.

Jaraback, 1956 and Solberg et al, 1975, demonstrated an immediate drop in EMG activity on wearing a stabilization splint with return to normal levels on its removal. Clark et al, 1979, found no uniformity in patient response to stabilizing splints. For 25 TMJ patients treated for two weeks 52% showed

reduced EMG activity, 28% no change and 20% increased EMG activity.

Willamson and Lundquist, 1983, suggest anterior guidance of the splint has an important effect on the EMG activity of the musculature.

Wilkinson et al, 1992, in an uncontrolled investigation compared patterns of splint usage and found nocturnal wear was as effective as 24 hour wear for mainly muscle related pain. Nocturnal wear only was also recommended in an uncontrolled study by Davies and Gray, 1997.

Clinical studies using stabilization appliances frequently combine usage with other modes of therapy including occlusal adjustment and prosthetics, (Franks, 1965, Zarb and Thompson, 1970, Agerberg and Carlsson, 1974, Magnusson and Carlsson, 1980). Combined therapy then results in 70-90% clinical success, (Clark, 1984). When used as the only form of therapy similar results are quoted, (Carraro and Caffesse, 1978, Gohrian and Neff, 1980, Okeson et al, 1982, Tsuga et al, 1989).

Carraro and Caffesse,1978, is a case series of 170 patients. Splints were worn full time apart from meal times. 82% of patients responded positively to therapy. 37% were cured and 45% improved. Pain symptoms were easier to resolve than dysfunctional symptoms. Clicking being the most difficult to eliminate.

Gohrian and Neff,1980, looking at a series of 17 patients treated with occlusal splints day and night for 3 weeks to a year, reported an overall 84% favourable response in relief of symptoms.

Okeson et al, 1982, in a case series selected 33 patients from a TMJ clinic population and treated them with a maxillary stabilization appliance for one month. Again 85% (28/33) showed decreased observable pain scores and improved interincisal opening.

Tsuga et al,1989, described a series of 30 selected cases, with more than 2 major symptoms of TMJ pain, clicking or limitation. Patients wore appliances for 13 weeks.

87% responded favourably to therapy and 50% had complete relief of pain after 4 weeks ($p<0.01$) suggesting good short term effectiveness. However, as with all case series it is impossible to determine whether improvement is due to treatment alone. Controlled studies comparing the stabilization occlusal splint with a comparison or control group therefore require examination. The first two studies showed no superiority for occlusal appliances but both were nonrandomised. Green and Laskin, 1972, compared occluding and nonoccluding splints but concluded both to be equally effective. Nemcovsky, 1992, compares alprazolam, splint or combined therapy again with all treatments equally effective. For more reliable evidence of efficacy one must investigate randomised controlled clinical trials.

Lundh et al, 1992, compares a group of patients receiving occlusal splints to a group of patients receiving no treatment. In the later group patients are simply placed on a waiting list. The results reported both groups improved similarly. However, patients were not prohibited from taking other treatment and were provided with pain medication as required. The no treatment group may therefore have been benefiting from other effective therapy. In preference to a no treatment group randomised studies comparing alternative treatment should therefore be considered.

Okeson et al, 1983, investigated intraoral splints versus relaxation techniques. Oral appliances were reported the superior form of treatment. However, this finding was not supported in a later study, (Winocur,2002).

Linde et al, 1992, compares oral appliances versus TENS with superiority of the intra oral appliances . However, the efficacy of TENS is in question. Dao et al,1990, showed TENS to have no advantage over placebo in which case intraoral appliances may have been unwittingly compared to placebo.

List et al., 1992, compares intraoral appliances versus acupuncture and found both to reduce symptoms but acupuncture to be more effective. Unfortunately, the authors noted that random assignment failed to equate the pre-treatment group differences which decreases the inference of treatment efficacy.

Dahlstrom et al,1982, compared stabilization appliance with EMG biofeedback and found no significant differencein the improvement of dysfunction between groups.

Turk et al., 1993, again compares intraoral appliances versus biofeedback. However, oral appliances were found to be more effective at 6 weeks but not at 6 months. Treatment compliance was not monitored however and hence a discontinuation in splint wear may have occurred at some point before the 6 month review.

In place of alternative treatment, placebo treatment has been used. A placebo is used in an attempt to equalize patient's expectations of improvement and can be used to blind patients and staff to treatment grouping. Marbach and Raphael, 1996, explains a 'placebo' bite plane to be a hard acrylic splint covering only the palate with no active occluding surface but believed by the patient to be equally effective to a standard appliance.

Greene and Laskin, 1972, compared occluding and nonoccluding splints and found both equally effective with 40% improvement with a placebo bite guard, but this study was non randomized.

Rubinoff et al., 1987, randomly assigned 28 patients to either conventional or palatal splint therapy with two clinicians one providing therapy and a second blind examiner. It was found the conventional splint appeared to relieve clinical signs of dysfunction more effectively but was statistically insignificant but both splints relieved symptoms equally and concluded no treatment outcome difference between groups. Unfortunately sample

sizes were small and random assignment failed to equate groups with regard to pre-treatment symptoms.

Marbach and Raphael, 1996, calculates that pre-treatment levels in the active splint group were significantly lower initially. Magnitude of symptom reduction was therefore relatively limited creating difficulty in demonstrating any significant pain reducing effect in the conventional therapy group.

Dao et al, 1994, does effectively equate groups by random assignment of 63 patients prior to treatment. There were three groups a palatal splint worn 24 hours a day, a hard acrylic appliance worn 24 hours a day or 30 minutes a day. In conclusion all treatments were equally effective at reducing pain related symptoms at 10 weeks. At 5-7 weeks treatment however the active appliance was significantly more effective in reducing pain intensity at rest. This may reflect decreased efficacy of the appliance after 7 weeks or poor compliance with the patients no longer wearing the appliance 24 hours a day after 7 weeks. Feinmann and Harris, 1984, found subjects wearing an oral appliance decreased to only a third compliance after 9 weeks of therapy. Another factor to consider is the value of the palatal splint as a placebo. At present the precise physiologic mechanism of splint therapy is still unclear with multiple theories to explain splint action. Palatal splints would not have an active effect if functional unloading or muscle hyperactivity were the active mechanisms. However, this may not be the situation if one considers the cognitive awareness theory of an appliance as proposed by Clark, 1984.If the cognitive awareness theory is considered to contribute significantly to the action of splints then palatal splints might in fact be exerting this unintentionally. A palatal splint or indeed any form of appliance can not be regarded as a valid placebo. Marbach and Raphael, 1996, suggested studies employing palatal splints may inadvertently have over controlled for the active treatment component

simply levelling treatment outcome on cognitive factors and so missing any potential benefit of the conventional appliance. Design of a placebo that effectively controls for the active component of splint therapy, is extremely difficult unless an underlying mechanism of splint action can be scientifically determined by future research. In the meantime, short term efficacy of splint therapy was indicated in the well designed studies of Turk et al, 1993 and Dao et al., 1994, but not long-term. Dao et al, 1994, explains that although the study questions the long-term therapeutic value of splints at present there is no clear evidence that any other treatment has a better curative capacity. A systematic review of RCT's for occlusal treatment found splint therapy to be superior to 3 control treatments, comparable to 12 and superior or comparable to 4 passive controls, (Forssell et al, 1999). Raphael et al, 2001, suggest a modest effect in symptom improvement for localised pain compared to placebo however; two further studies suggest more significant results. Wahlund, 2003, found occlusal appliances in TMD therapy of adolescents to be superior to combined relaxation training and brief information $p<0.05$ In a further randomised controlled trial, stabilization appliances were shown to be more effective in myalgic TMD for reduction in signs and symptoms, (Ekberg,2003).

Compliance in wearing appliances including careful examination to detect any negative effects of therapy needs further investigation in well controlled randomised clinical trials. Until a definitive therapy is established for treating Facial Arthromyalgia,(TMD) stabilizing splints remain a useful, conservative and reversible form of adjunctive therapy in TMJ management.

4.6 **Occlusal adjustment**

This is an invasive and irreversible form of therapy which involves occlusal equilibration or alteration of the occlusion by prosthodontic or orthodontic repositioning. A systematic review of randomised controlled trials of occlusal treatment was published by Forssell et al, 1999.Occlusal adjustment was found comparable to two and inferior to one control treatment and comparable to passive control in one study. Tsukiyama et al, 2001, in an evidence-based assessment of occlusal adjustment again found usage to be unconvincing due to lack of experimental evidence.

Most recently, Koh and Robinson, 2004, in a comprehensive review of the literature and meta analysis found no evidence for treatment or prevention of TMD with occlusal adjustment and advised clinicians against recommending such management.

4.7 **Surgical therapy**

Although non compliant with the recommendations of non-invasive and conservative procedures, surgery does have a role in the management of specific TMJ disorders. Ankylosis, growth disorders, neoplasia and some trauma obviously require surgery, yet indications for the more common disorders of recurrent dislocation, joint internal derangement and osteoarthritis are less clear. Careful case selection is required to avoid the potential complicating factors particularly psychological issues,(Poker and Hopper,1990).

Clinical symptoms often do not correlate with imaging studies. TMJ arthrography and nowadays MRI, magnetic resonance imaging, is of value in depicting disc position, (Rao, 1995). However, there is variable position of the normal meniscus, 30% of asymptomatic patients have abnormal disc position on MRI and 25% of symptomatic

patients have normal disc position,(Westesson et al, 1989). Excessive reliance on the diagnostic value of imaging can lead to over diagnosis of internal derangement and hence over treatment. More emphasis should therefore be placed on the history and clinical examination than results of imaging studies alone,(Buckley et al,1993).

TMJ surgery includes a range of procedures from the relatively minor Arthrocentesis or joint lavage, closed arthroscopy to open joint surgery of arthrotomy, joint exploration, major joint reconstruction and extraarticular procedures.

Arthrotomy is only indicated in patients who meet the surgical criteria of advanced TMJ disease,(Okeson,1996). Numerous approaches to the TMJ are described but a preauricular incision is most commonly used with exposure of the superior and if required inferior joint spaces,(Quinn,1998).

Arthrotomy provides scope for a range of procedures from the simple lavage and debridement to disc repositioning, discectomy or arthroplasty bone recontouring. In the past, condylectomy, high condylar shave and condylotomy were also performed. A modified condylotomy or intraoral vertical ramus osteotomy is a closed procedure where the joint is not entered,(Poker and Hopper,1990).

Complications of surgery include occlusal alterations, facial nerve damage, pain , in the past failed implants, fractures or dislocations of the condyle or condyle-disc relationship,(Okeson,1996).

Arthroscopy of the TMJ was first described by the Japanese in 1975 before spreading to Europe and the USA,(Ohnishi,1975). Initially described as a diagnostic technique therapeutic applications were later developed,(Hollmlund and Helsing,1988, Dolwick,1997)

Indications for arthroscopy might include internal derangement pain, decreased mouth opening and clicking, degenerative joint disease, synovitis, hypo and hyper mobility, (Nitzan,1990Alpern et al,1997,).

Diagnostic and therapeutic operative procedures include lavage of the joint space with saline, ablation of fibrous adhesions in the upper joint space for treatment of closed lock, painful limited mouth opening, anterior disc release with restoration of mobility and position by dissection, cauterisation or laser treatment, biopsy of lesions and finally instillation of medication in the form of steroids, hyaluronate or morphine. The procedure is normally performed under GA but compared to open joint surgery is minimally invasive with less surgical trauma, lower morbidity, faster healing time and more rapid recovery,(Bronstein,1989, Dolwick,1997). It is dependent however not only on surgical skills but expensive equipment and technology, arthroscope, light source, TV camera and monitor. Arthroscopy allows direct observation and sampling of the joint tissues and the three dimensional joint space is viewed on the two-dimensional screen image. This may reveal capillary hyperaemia or fibrous adhesions. Incision of adhesions, debridement and lavage can then be performed and the surgical site closed with suture and steri strip dressing.

In contrast to arthroscopy, arthrocentesis involves simple intra-articular irrigation or lavage of the TMJ. Reports on the success of arthrocentesis have been favourable. It has been suggested that this method may be as effective as arthroscopy particularly when used with joint mobilization in the treatment of acute onset closed lock and to relieve disc adhesions in the glenoid fossa,(Nitzan et al,1991, Dimitrioulis et al,1995).

It is simple to perform, equipment is inexpensive and the procedure is far less invasive and can be carries out under LA,(Nitzan,1991). The success of arthrocentesis or arthroscopy in management of closed lock suggests restricted gliding movement of the

condyle over the articular eminence may be due to reversible adhesion of the disc to the glenoid fossa caused by a vacuum effect or alteration in synovial fluid, Quinn,1990). Although surgical management of TMJ dysfunction is quoted in retrospective studies as being effective in decreasing pain and increasing range of motion in 80% of patients, long-term randomised controlled trials are limited,(Okeson,1996). In one RCT arthroscopy was not significantly better than physical therapy in treatment of restricted jaw movement and pain from articular disease, (Stegenga et al,1993). TMJ surgery is only suitable for selected cases due to potential complications, the high prevalence of behavioural and psychosocial contributory factors in TMD and the wide availability of non-invasive management,(Okeson,1996). Surgical intervention should be reserved for a small percentage of patients with significant persistent pain and dysfunction with demonstrable internal disc derangement (Harris et al ,1995).

4.8 PHARMACLOLOGICAL THERAPY

Reported medical therapy in the management of TMD include simple non-opioid analgesics, anxiolytics and muscle relaxants, antidepressants, corticosteroids, opioids and even botulinum toxin. A qualitative systematic review of pharmacological interventions in the treatment of TMD suggests more, large RCT's are required to determine efficacy,(List et al,2003).

4.8.1 Non opiod analgesics

This group constitutes a variety of drugs with diverse chemical structure but similar therapeutic effect. Well-established in acute pain, side effects are negligible when dosage recommendations are followed (Kehlet, 1999). Long-term administration however, is well documented to result in serious toxicity and adverse effects, (Holovet

et al 1991, Laporte et al, 1991, Kaufman et al, 1993). Justins, 1996, found NSAIDs and paracetamol, only have proven benefit in chronic inflammatory musculoskeletal pain. Treatment benefit in generalised chronic pain must only be seriously considered in relation to toxicity. Paracetamol, although widely used, has an analgesic effect 20-30 % lower than NSAIDs, (Weibalch and vonAhanm 1995, McQuay et al 1997, Moore, 1997). NSAIDs are analgesic for mild to moderate acute pain, antipyretic and anti-inflammatory, (Greene, 1991, Hargreaves, 1987).

Table 4a: Simple (Non opioid) analgesics

- **Analine derivatives** – Paracetamol
- **Salicylates** – Asprin (Acetyl salicylic acid)
- **Non steroidal anti inflammatory drugs (NSAIDs) (COX-1 inhibitors)**
  - Indoles – Indomethacin
  - Proprionic acid derivatives – Ibuprofen, Naproxen, Ketaprofen, Lorioxicam, Mefanamic acid and Tolfenamc acid.
- **COX-2 inhibitors** - Refocoxib, Vioxx

Despite large numbers of trials published on NSAIDs systematic reviews reject the majority leaving an almost inadequate number of acceptable studies to allow conclusive results. Assessment is therefore based on adverse effect profile and pharmacokinetic considerations rather than superiority as an analgesic,(Gowley, 1999).

A systematic review of NSAIDs in Rheumatoid and Osteoarthritis in acute and chronic pain (Moore, Pendrey, Tamer and Emery,) failed to identify a particular NSAID which consistently provided superior analgesia compared to others. Development of newer NSAID's did not significantly improve efficacy or decrease side effects, (Merry and Power, 1995).

4.8.2 **Route of administration**

NSAIDs are administered by a variety of routes IV, IM, PR, O, topical. No advantage was demonstrated in preference to the standard oral route (Tramer et al,1988). The only exception was the application of topical drug in chronic and acute pain where there was decreased incidence of G I side effects compared to oral administration but similar analgesic effect for both, (Moore,1998).

4.8.3.**Side effects**

A meta analysis of 16 controlled studies suggest a threefold increase in the risk of developing adverse GI events in NSAID users, compared to controls with greater risk over 60 years of age,(Gabriel et al, 1991).

The major toxic effect of NSAIDs are gastroduodenal damage variable incidence of gastric ulcers (18-47 %) and duodenal ulcers (2-8%), (Roderick et al,1993, Stalnikowicz and Rachmilewitz,1993). Misoprostol significantly reduces the incidence of gastric ulcers with a similar effect to ranitidine on duodenal ulcers. Kidney blood flow is altered by NSAIDs by interference with PGE synthesis in the kidney affecting autoregulation of blood flow and glomerular filtration, (Clive and Stoff, 1984).

In chronic NSAID use the inhibitory effect on kidney PGE production can lead to acute, reversible kidney failure in 0.5-1 % of patients (Welton and Hamilton, 1991).In patients with a pre-existing decreased kidney blood perfusion, haemodynamically mediated acute kidney failure may be a significant side effect. A nine fold increase risk of end stage kidney disease was reported in a retrospective analysis. In demonstrated an association between patients with end stage kidney disease requiring haemodyalisis and chronic NSAID use (>5,000 tablets per lifetime), (Perneger et al, 1994).

Pharmacological effects are achieved by inhibiting prostaglandin (PGE) synthesis via the action of the enzyme cycloxygenase (COX) of which two isoforms exist, COX -1 and COX-2. NSAIDs are COX-1 inhibitors. The COX-1 isoform is present in most tissue and consequently NSAIDs exert a widespread action, not limited to the site of injury. The result is considerable pharmacological effects including alteration to the normal function of the G I mucosa and kidney blood flow.

4.8.4 COX-2 inhibitors

The COX-2 enzyme is induced in inflamed tissue by the action of cytokines and cellular mediators. Inhibitors of COX-2 should hence provide analgesia with fewer side-effects, (Kurumabeil et al, 1996). The introduction of COX-2 inhibitors were promising to be beneficial in acute short-term pain treatment and observations in patients with chronic inflammatory pain indicated reduced side effect incidence with maintained analgesic efficacy,(Hawkey, 1999).However, concern has recently risen over the safety profile in relation to cardiotoxicity and several COX-2 inhibitors have been withdrawn, (Drazen ,2005, Luo et al,2005.).

4.8.5 Combined or balanced analgesia

The rationale of combined analgesics was to improve the efficacy and decrease side effects. The aim was to achieve this by combining smaller doses than are usually required of each drug. A NSAID or paracetamol are combined with a weak opioid for example codeine or propoxyphene.

Different sites of action for each drug relys on a synergistic or additive analgesic response. Moore, 1997, found in the treatment of acute pain, a statistically significant analgesic effect was achieved with codeine and paracetamol compared to paracetamol

alone, one additional patient in nine obtaining 50 % pain relief from the combination drug. Eisenberg, 1999, in a meta analysis of NSAIDs alone or in combination with weak opioids, in the treatment of cancer pains revealed the same extent of analgesia for both formulations. Weak opioids were required in substantial dosage before an observed additional analgesic effect could be achieved suggesting little benefit with all the disadvantages of high dose stronger opioids. This queries the role of the fixed combination of NSAID and opioids for use in any pain condition and questions the validity of stage two in the WHO analgesic ladder. (McQuay, 1999).

4.8.6. NSAID treatment of chronic orofacial pain and TMD

In this field there are very few well controlled studies, but benefit has been reported, (Truelove, 1994). Recommendations on usage are often extrapolated from cases of chronic inflammatory conditions such as arthritis. It is suggested a short trial of a NSAID be considered for patients with an apparent inflammatory component to the pain, such as acute symptoms of TMD associated with trauma, (Dionne 1997). Two placebo controlled studies suggest NSAIDs to be ineffective in the treatment of chronic orofacial pain. There was no therapeutic advantage for the NSAID Piroxicam 20mg daily compared to placebo in 28 patients with TMD, (Gordon et al, 1990). Likewise chronic orofacial pain of myogenic origin was found to respond in a similar manner to placebo or the NSAID, Ibuprofen, 2,400 mg daily for four weeks,(Singer et al ,1987). Juniper, 1993, advocated the use of NSAIDs during acute exacerbations of pain. Yuasa et al, 2001, found combined NSAID and mouth opening exercises over 4 weeks to produce objective improvement in 60% of TMD cases with disc displacement without reduction compared to 33 % improvement in a non treatment control group.

4.8.7. Opioids in chronic non-malignant pain

Long-term administration of opioids for non-malignant pain is controversial and up until 10 years ago was felt inappropriate,(Hardy, 1991). Concern centres around the potential for addiction and withdrawal in terms physical dependence and tolerance requiring an increased dosage. In a therapeutic context the use of sustained release formulations minimise cyclic fluctuations whilst maladaptive behaviour should not occur if monitoring of dosage is properly regulated. A survey of 1,912 randomly selected physicians in the USA revealed widespread prescribing in medical practice with careful adherence to the stringent protocols required, (Turk et al, 1994).
When other treatment has failed, several recent studies do therefore support usage in chronic non malignant pain. Zenz et al, 1992, in an open study of 100 chronic pain patients on sustained opioids revealed 51% good pain relief and 28% partial pain relief with no respiratory depression. Ark install et al, 1995 in a double blind controlled trial of 46 patients showed significant analgesia and pain improvement on the disability index with sustained release oral codeine but higher incidence of nausea than with placebo. Moulin et al 1996, led a randomised double blind crossover study of patients non responsive to codeine, NSAIDs and antidepressants. Oral morphine 60 mg bd produced significant pain relief with little effect on cognitive function or memory. Opiates are once again clearly recognised in the control of chronic pain, (Mac Pherson, 2000, IASP, 2000).

4.8.8. Opioids in TMD

Intra articular morphine has been used in a randomised double blind controlled study showing a significant increase in pain threshold in diseased joints,(List, 2001). No direct evidence based evaluation has been made of long-term administration of oral

opioids for patients with severe TMD. Treatment at present hence requires careful patient selection to avoid those with a personality disorder or drug seeking behaviour and establishment of a clear patient contract with careful monitoring to regulate dosage and to avoid side effects or escalation in dosage. Carefully selected cases have been shown to have excellent analgesic results, (Harris, 2000). Further evaluation is required in randomised controlled trials for severe intractable TMJ pain for example post TMJ surgery and having first exhausted the alternative medical therapies.

4.8.9. **Benzodiazepines (Anxiolytics and muscle relaxants)**

Diazepam 2-5mg at night can reduce nocturnal bruxism and acute TMD pain in short term administration (Rugh, 1988). Similarly, Clonazepam reduces painful TMD, head and neck symptoms with nocturnal doses of 0.25-1mg as demonstrated in a 30 day double blind trial of a small sample of 10, (Harkins, 1991).

Singer et al, 1987, found significant pain relief with diazepam compared to ibuprofen and placebo in a double blind trial of 39 chronic myalgic orofacial pain patients. Interestingly, there was also a tendency towards improvement in depression and anxiety, although results should be considered cautiously in view of the limited numbers of 9-11 per group.

Alprazolam, a more potent anxiolytic than diazepam, was found to decrease local pain and muscle tenderness and increase mandibular movement without reduction in joint sounds. However, results also suggest that the flat plane occlusal splint to be as effective as alprazolam with no significant improvement in symptoms when combining splint and alprazolam, (Nerncorsky et al, 1992).

In view of the longstanding professional concern of the potential for dependence, sedative effects and possible exacerbation of depression, this family of drugs should

only be considered with caution for short term administration in acute episodes of myogenous pain and contraindicated for long-term use in chronic conditions (Dellemijin, 1994, Dionne, 1997)

4.8.10.**Corticosteroids**

Corticosteroids as powerful anti-inflammatory agents have been administered by injection and topical application in cases of osteoarthritis, myalgia and trismus but long term results are equivocal (Wenneberg,1991,Dionne,1997).There is no evidence to support the use of systemic corticosteroids and intra articular injections may reduce pain symptoms but repeated injections can cause significant tissue destruction, (Dennuci,1996).

4.8.11. **Botulinum toxin**

Botulinum toxin injections were a suggested treatment for TMD, (Freund, 2000). However, a randomised controlled trial did not support the use of botulinum toxin A in patients with moderate to severe chronic myalgia pain. Results concluded patients receiving treatment had reduced jaw opening compared to a placebo group, (Nixdorf, 2002).

4.8.12 **Antidepressants - In the treatment of chronic orofacial pain**

Antidepressant drugs have been used in the management of chronic pain for nearly 40years, since the early 1960's. Despite this length of time, no antidepressant in the UK has a product licence specifically for this purpose (McQuay and Moore 1999).The therapeutic recommendations from the biomedical literature "supports the clinical use of antidepressants for chronic non malignant pain when other treatment has failed or

depression accompanies pain" (Dionne 1997). However, depression is not always associated with pain. In four separate reviews of controlled studies, looking at the use of antidepressants for pain management, analgesic effects were found to be mainly independent of antidepressant activity (Egburke and Chaffee 1990, Magni 1991, Onghena and Van Houdenhove 1992 and McQuay 1996).This suggests a specific analgesic action in addition to antidepressant or sedative effect of these drugs.

4.8.13 Background - Association of pain and depression

The concept that pain and depression may share a common biological pathogenesis has led to much debate on whether certain individuals may be more vulnerable to the development of pain or depression.

Biological systems markers shared by chronic pain and or depressed patients include: hypercortisolaemia, abnormal dexamethasone suppression test and low serum and urine melatonin levels (von Knorring, 1988). Tyramine conjugation excretion deficit, was used as a trait marker for endogenous depression (Aghabeigi et al,1993). This was also found to be present in patients with chronic TMJ and orofacial pain even in the absence of depression (Hale et al,1986).

Chronic pain and depression as different representations of a similar central neurochemical alteration was first suggested by (Sternbach 1976). It was proposed that pain is inhibited by adequate circulating levels of the monoamines, NA nor adrenaline, 5HT (serotonin) and possibly DA (dopamine) within the brain.

Chronic pain was believed to deplete brain neurotransmitter levels of 5HT, particularly in the region of the dorsal raphe nucleus. Almay et al, 1987, showed patients with idiopathic pain syndromes exhibit low concentrations of serotonin metabolites in their CSF. This low level does not however alter during the course of the condition and may

represent a marker of increased risk of developing a chronic pain syndrome (von Knorring, 1988). The low level may also explain lack of analgesic with opiates, the association of chronic pain with depression and effectiveness of antidepressants which increase the level of this neurotransmitter.

Antidepressant drug action involves increased monoamine neurotransmitter availability in the synaptic cleft, with alteration in density and functional responsivity of both or either adrenergic and serotonergic receptors, (Palozidou, 1997, Pettergill, 1997, Sudoh, 2002). Neurotransmitter breakdown is prevented in the case of MAOI whilst neurotransmitter reuptake to the preganglionic neuron terminal is inhibited with the TCAs and SSRIs.

4.8.14 SSRI (Selective serotonin reuptake inhibitors)

Serotonin (5, hydroxytryptamine, 5HT) is a monoamine. Wilcox, 1999, in reviewing serotonin, explains that intrathecal administration of serotonin in animals can either inhibit or stimulate nociceptive reflex dependent on dosage and species. Similarly activation of descending serotonin releasing systems can elicit excitation or inhibition. It is suggested that the three distinct serotonin receptor subtypes 5HT 1D, 5HT 2, 5HT 3 may account for these variable responses. The 5HT 1D receptor subtype mediates selective inhibition of nociceptive neurones (El Yassir et el 1998, Alhader and Wilcox 1993).

Following identification of serotonin receptors, production of selective agonists and antagonists were developed with antidepressants and analgesic action. Blockade of serotonin reuptake may account in part for the analgesic activity of TCA and SSRI drugs (Kahl and Wilcox 1984, Hurang and Wilcox 1987).

SSRI (Selective serotonin reuptake inhibitors) have become the most popular class of drugs in this group. Fluoxetine was the first SSRI to be introduced in the USA but only became available in Europe in 1983. Large multicentre placebo controlled studies of fluoxetine in the treatment of depression revealed antidepressant efficacy similar to the TCA, (Montgomery, 1989).

Although efficacy is not necessarily superior to the first generation antidepressants, MAOI and TCA, there appears to be a reduced side effect profile, better tolerance and less toxicity in overdose (Leonard 1993).

Examining placebo controlled studies with a reference comparator or standalone active comparator studies using TCA such as amitriptyline or dothiapine report no significant difference between groups. Occasionally studies report increased efficacy with SSRI (Feigher et al, 1989, Muijen et al, 1988) or decreased efficacy (Anderson et al, 1986). Meta analysis of databases is also used to assess relative efficacy. Fluoxetine has similar efficacy to the TCAs (Pande and Sayler, 1993) as do SSRIs in general (Montgomery et al, 1994). There are no direct comparative studies between SSRIs so categorically one is not more affective than another.

4.8.15 **Pharmacokinetics and pharmacodynamics of SSRI.**

The SSRIs vary in their selectivity and potency for 5HT receptors. Fluoxetine is converted to the active metabolite nor-fluoxetine, which is three times more selective and potent for serotonin. Clinical efficacy is hence more important than fluoxetine. Fluoxetine itself is rapidly absorbed and distributed with a time to peak plasma concentration of 2-8 hrs. Plasma levels achieved with SSRIs is subject to wide interindividual variation. Although reports suggest poorer response associated with high

plasma concentrations of some SSRIs the drugs are not associated with a narrow therapeutic window (Altamura and Montgomery, 1990, Montgomery et al, 1981).

Clearance times vary, fluoxetine remaining in the blood stream for the longest with a ½ life of 1-3 days, whilst the active metabolite nor fluoxetine has a half life of 7-15 days. Although persistence of the drug into the blood stream has advantages when there is irregular compliance there is an increased risk of drug interaction when discontinuing and changing to an alternative drug.

Combined SSRI and MAOI can lead to serotonin syndrome which is potentially lethal and can also lead to rapid death from hyperthermia (Sternbach, 1991). An SSRI should only be started after 2 weeks of stopping MAOI and conversely MAOI should be started only after at least 5/52 of stopping fluoxetine.

A variety of other drugs have been reported to interact with the SSRIs. Several SSRI'S including fluoxetine are metabolised by the P450-P2-D6 cytochrome system. Several antiarythmics, beta blockers, neuroleptics and TCAs such as amitriptyline, nortriptyline and domipramine are also metabolised by the same system. Consequently interactions between SSRIs and TCAs have been reported due to increased drug plasma levels (Aranow et al, 1989, Bauman and Bertschy, 1993, Vandel et al, 1992). This is less important with SSRIs but TCAs have a narrower safety margin and may already be used at doses close to the toxic limit.

Inhibition of the enzyme system more rapidly occurs in certain individuals due to genetic polymorphism of the system in 7% of Caucasians who are poor metabolisers of these drugs. The required caution with concomitant therapy hence becomes even more persistent .The major clinical advantage of SSRIs is the improved side effect profile and better tolerance.

4.8.16 **Safety and Tolerability. (Side effects).**

SSRI'S are less sedative than TCA with few antimuscarinic effects and low cardiotoxcity. They do not cause weight gain and in some cases result in weight loss. The most common side effects are gastrointestinal disturbance (nausea, diarrhoea and vomiting). This is usually mild decreasing with continued treatment but dose dependent, higher doses often causing nausea. Early in treatment a few patients may experience anxiety or agitation related to the 5-HT 1C agonist properties of fluoxetine (Zhang, 1993). Extra pyramidal movement disorders can occur with SSRIs including Fluoxetine due to the role of serotonin in dopamine autoregulation. (Baldwin et al,1991,Bouchard et al,1989,Brod,1989,Levinson et al,1991,Tate,1989).

4.8.17 **Optimum dosage.**

Optimum therapeutic dosage relies on observing the effect of drugs in animals, dose titration studies and fixed dose studies.

In dose titration, the dose is increased to maximum toleration at which a response is observed. However, due to delayed response a low dose may be attributed to a later higher dose. The unnecessary high dose may give rise to increased side effects without enhancing efficiency.

Table 4b: Studies investigating the effect of Fluoxetine versus placebo

Study	N	Results
Wernicke et al, 1987	336	Fluoxetine 20mg > Placebo Fluoxetine 40mg > Placebo
Wernicke et al, 1987	354	Fluoxetine 5mg > Placebo Fluoxetine 20mg > Placebo Fluoxetine 40mg > Placebo
Fabre abd Crimson, 1985	37	Fluoxetine > Placebo
Rickels et al, 1986	38	Fluoxetine > Placebo

The most reliable studies are the fixed dose comparing response to a range of doses given in a fixed dosage regimen. Initial studies of fluoxetine used 80mg/day maximum dose. Later fixed dose studies showed that 20mg and 40mg were significantly better than placebo. The 60mg dose although effective were associated with increased side effects and increased number of withdrawals from medication because of side effects (Wernicke et al, 1987). In a fixed dose study of 5mg, 20mg, and 40mg fluoxetine, all doses were found to be significantly better than placebo although a larger treatment effect was seen with 20mg and 40mg doses (Wernicke et al,1988). In long term studies, fluoxetine 20-40mg as prophylaxis, maintenance therapy was found to reduce the risk of new episodes of depression (Rosenbaum et al, 1993, Montgomery et al, 1988.).

4.8.18 **Optimal dosage in pain relief.**

There is some controversy regarding optimal dosage of antidepressants to achieve analgesia. Onghena and Van Houdenhove, 1992, in a systematic review showed similar analgesic properties were obtained with lower than normal established doses of antidepressant drugs. If therapeutic effect of antidepressants were achieved through alleviation of depression, doses would be similar to those required to treat depression. However, if analgesia is achieved independent of the alleviation of depression then perhaps a lower dosage of antidepressant would be expected. McQuay et al, 1993, did not show this response. In a double blind multiple dose study he established a direct dose-response relationship, where 75mg amitriptyline provided improved analgesia and improved sleep in comparison to 25mg or 50mg.This was unrelated to mood but accompanied by significantly greater incidence of adverse effects. Zitman et al 1990,

also reports 75mg amitriptyline produced analgesia and improved sleep over six weeks but considered the effect only modest.

Sharav et al, 1987, however, demonstrated low dose amitriptyline (mean dosage 23.6mg) was as effective for chronic orofacial pain as a higher dose (mean 129mg), 75 mg - 150 mg being the usual daily antidepressant dose.

McQuay, 1992, also showed a daily dose of 25mg amitriptyline for three weeks was superior to placebo in patients with a variety of chronic non malignant pain.

Optimal dosage of SSRIs in pain relief remains unexplored at the current time.

Research on the efficacy of drugs specific to the serotonin receptors are limited in chronic orofacial pain. The serotonin anatagonist iprazochrome, was used to treat 30 patients with Atypical facial pain but results were equivocal, (Hampf, 1989). However, in a group of 178 chronic facial pain patients, Fluoxetine was found to decrease pain severity and distress in non depressed patients (Harrison et al, 1997).

4.8.19 **Historical perspective- Antidepressants in the treatment of chronic facial pain.**

(Webb & Lascelles, 1962) suggested orofacial pain might result from an underlying depressive disorder. Early studies proposed a direct correlation between depression and orofacial pain. A double blind controlled trial of 40 AFP patients showed the efficacy of phenalzine, Nardil, a MAOI (Lascelles, 1966). 27 patients with tension headache and depressive symptoms were found to have more relief from amitriptyline a TCA than placebo (Lance & Curran 1964) Similarly tension headache patients with concomitant anxiety and depression responded well to amitriptyline at 8 weeks, (Okasha et al 1973).The compound carbamezapine (Tegretol) which has the same tricyclic nucleus as imipramine, a tricyclic antidepressant, was found to have both anticonvulsant and analgesic properties. (Evans, 1973).

Tricyclic antidepressant drugs for the treatment of chronic orofacial pain was recommended by (Harris,1974).An uncontrolled trial of the TCA (Amitryptyline) was found to be of benefit in 5 out of 8 patients in a paper published by (Gessel,1975). A two centre double blind controlled trial of Dothiepin was found to relieve pain in 71% of patients at 9 weeks (Feinmann, 1984). Withdrawal of the drug at 6 months led to relapse and necessitated reintroduction of dothiepin to control pain. Long-term follow-up at 4 years after initial treatment showed pain improvement can be maintained over time. It was suggested that long-term administration may be required for long-term symptom control, (Feinmann, 1993).

Sharav et al, 1987, demonstrated low doses of 25mg were as effective as high doses of 100mg of amitryptyline in the reduction of pain, independent of antidepressant effect. Harrison et al.1997, demonstrated the efficacy of the SSRI, fluoxetine in the treatment of mixed chronic orofacial pain. In the three later studies pain and depression were found to be independent, (Feinmann et al,1984, Sharav et al,1987, Harrison et al ,1997). Low dosage tricyclic antidepressant efficacy for chronic pain relief, independent of depression, was later reiterated (McQuay, 1996, Plesh, 2000).

4.8.20 **Randomised controlled trials of antidepressants in chronic orofacial pain**

There are an estimated 50 placebo controlled trials in the literature regarding the use of antidepressants in chronic pain. However, only 6 of these studies evaluated usage in orofacial pain and provide the most relevant information at the present time. (Lascelles, 1966, Feinmann, 1983, Sharav, 1987, Harrison, 1997, Plesh, 2000, Raigrodski, 2001) The first of these studies was published over 30 years ago.

4.8.21 **Conclusion**

None of these studies were specifically investigating the effect of antidepressant medication in FAM (TMJD). All studies contained groups of patients with a heterogeneous mixture of chronic orofacial pain conditions. Since no randomised controlled trials existed in the mid-1990's which concentrated solely on TMD, a need was identified to investigate the efficacy of antidepressant medical therapy versus physical therapy in the management of TMD.

Table 4c: Antidepressant medication in chronic orofacial pain – controlled trials					
Author	**Year**	**Medication**	**Design**	**Diagnosis Number of subjects**	**Pain improvement**
Lascelles et al	1966	Phenalzine (Nardil) MAOI 15mg tds vs placebo	Cross over trial 4 weeks	Mixed heterogenous Chronic facial pain (depressed) N=40	At 4 weeks. Improvement in: Pain 75% Depression 30%
Feinmann and Harris	1984	Dothiepin (dose titration method) vs placebo vs soft acrylic bite guard	Parallel groups 9 weeks, 6 months and 4 years longterm follow-up	Mixed heterogenous Chronic facial pain (depressed/nondepressed) N=93	At 9 weeks. 71% pain free.
Sharav et al	1987	Amitryptyline 30mg,150mg vs placebo	Cross over trial 4 weeks	Musculoskeletal facial pain N=28 (depressed/nondepressed)	Low dosage as effective as high dosage in reduction of pain.
Harrison et al	1997	Fluoxetine 20mg vs placebo vs CBT and fluoxetine vs CBT and placebo	Parallel groups 3 months 6months and 9 months and 1 year follow up	Chronic (atypical) facial pain and Facial Arthromyalgia (TMD) (depressed/nondepressed) N=181	Pain reduction at 3 months with fluoxetine compared to placebo and maintained when drug therapy ceased (16-33%)
Plesh et al,	2000	Amitryptyline 10-30mg	Pilot study (no control) 6 weeks and 1 year follow up	TMD (2 groups) Myofascial and myofascial and TMJ pain N=25	Effective in reducing pain and significant improvement in global treatment effectiveness
Raigrodski et al	2001	Amitryptyline 25mg	Cross over trial 4 weeks	Bruxism and pain N=10	No significant reduction in pain intensity ($p>0.05$) Significant reduction in perception of stress ($p<0.05$)
Forssell et al	2004	Venlafaxine 75mg vs placebo	Cross over trial Two 4 week periods with a 2 week 'wash out'	Chronic atypical facial pain N=30	Moderate effect. No significant reduction in pain severity but moderate pain relief as more additional analgesics consumed in placebo group.

MATERIALS AND METHODS

CHAPTER V AIMS AND OBJECTIVES

5.0 Aims and Objectives of the study

The aims of the investigation are:

Primary aims:

(1) To compare medical (antidepressant medication) and physical (occlusal appliance) therapy in the management of TMD, both alone and in combination, using a randomised, placebo controlled trial.

Secondary aims:

(2) To describe the characteristics of those referred to a TMD research study.

(3) To examine the character of TMD pain and associated clinical features.

(4) To describe the psychosocial features associated with TMD.

(5) To measure amelioration or deterioration in pain severity, interference, frequency, signs, symptoms, co morbid pain conditions, depression and other psychosocial factors.

(6) To explore differences in characteristics and response of subgroups in the TMD cohort: (i) with or without depression, (ii) high or low levels of pain at baseline (iii) those responding to therapy.

(7) To examine adherence and adverse events of therapy.

(8) To examine the post study effect on outcome during follow-up at six and nine months.

The objectives of the investigation are:

(1) To evaluate, using a RCT, with a primary outcome measure of >50% pain improvement, on a VAS.

(1a) The efficacy of medical therapy: a selective serotonin reuptake inhibitor: fluoxetine, Prozac in comparison to placebo.

(1b) The efficacy of physical therapy: a maxillary, Michigan style, stabilisation appliance in comparison to medical therapy.

(1c) The efficacy of the combination of medical and physical therapy in a RCT and to determine whether there is a synergistic effect from combining the two therapeutic modalities.

(2) To report the demographic and epidemiological features of the referral and study cohort and to compare the results to other TMD clinic populations.

(3) To describe the character, duration, severity, interference, frequency and pain free intervals of TMD pain, together with associated clinical features related to the orofacial region and co morbid chronic body pains, to determine which factors predominantly present in the diagnosis of TMD.

(4) To describe the psychosocial features of those with TMD, notably the patient's perspective of pain and impact on daily life, sensory and affective components of pain, depression and illness attitudes and beliefs, using self report questionnaires.

(5) To determine changes in secondary outcome measures; severity, interference, frequency, signs and symptoms of TMD, co morbid pain conditions and psychosocial features; post treatment.

(6) To undertake subgroup analysis in order to explore:-

(i) The influence of depression at baseline on outcome measures.

(ii) The influence of an initially high or low recording of pain severity on outcome measures.

(iii) The difference in baseline characteristics of responders and non responders to therapy.

(7) To examine adherence, reasons for nonadherence and adverse events experienced during therapy and to identify differences in these factors between therapeutic groups.

(8) To follow-up patients at six and nine months to determine if there is any maintenance or relapse in improvement post treatment.

The underlying themes of the investigation are stated in a series of hypotheses.

CHAPTER V HYPOTHESES

5.1 Hypotheses

To be derived from the RCT, primary outcome measures- Chapter VII

(1a) An SSRI (fluoxetine;Prozac) in daily oral doses of 20-40mg is more effective than placebo in the treatment of patients with chronic TMD.

(1b) A combination of an SSRI (fluoxetine;Prozac) and a bite guard are more effective than fluoxetine or bite guard alone in the treatment of chronic TMD.

To be derived from the baseline data of the referral study cohort – Chapter VI

(2) The demographic and epidemiological features of the study cohort, are consistent with the patient population seen within a secondary or tertiary TMJ clinic.

(3) The duration, character and location of TMD pain described are typical of a patient population seen within a secondary or tertiary TMJ clinic.

To be derived from the RCT, secondary outcome measures-Chapter VII

(4a) A significant improvement in the 'clinician recorded' intensity, interference and frequency of patient TMD pain, is only observed in the dual therapy group.

(4b) A significant improvement in the 'self recorded' impact of TMD pain on daily life; MPI severity, interference, life control and affective distress is only observed in the dual therapy group.

(4c) There is a significant difference in 'self recorded' BDI depression scores between the commencement and completion of the study.

(4d) There is a significant difference in 'self recorded' Kellner illness attitude and beliefs between commencement and completion of the study.

CHAPTER V HYPOTHESES

(5a) There is a significant improvement in the signs and symptoms of TMD between the commencement and completion of the study.

(5b) A significant improvement in the signs and symptoms of TMD are only seen in those wearing a bite guard.

(5c) There is a significant difference in the number of co-morbid pain conditions reported between the commencement and completion of the study.

(5d) A significant improvement in co-morbid pain conditions are only seen in those taking SSRI (fluoxetine).

To be derived from the post hoc subgroup analysis – Chapter VIII

(6a) A significant and measurable improvement in pain is only seen in those patients without depression at baseline

(6b) A significant and measurable improvement in pain measures are only seen in those patients with initially high pain scores

(6c) Clinical and pain history characteristics at baseline separate the treatment responders from the non responders.

To be derived from adherence and adverse events data recorded during the RCT- Chapter IX

(7) The four therapeutic groups were equally adherent to therapy

(8) There was no significant difference in adverse events between active and placebo medication

To be derived from post RCT follow-up analysis- Chapter IX

(9) The improvement in pain measures at the end of the RCT are maintained at six and nine month follow-up.

5.1 Study Design

The intention was to conduct a randomised, double blind for drug treatment, controlled trial at the Eastman Dental Hospital (1996-1999) to assess the value of selected medical versus physical or combined therapy in the management of patients with chronic TMD. The referral cohort were assessed using self report questionnaires, clinical history and examination to determine diagnosis. Patients eligible for inclusion and who consented to treatment were randomly allocated to one of four intervention groups, (table 5)

Table 5: Four intervention groups:

(1) Medical therapy – A selective serotonin reuptake inhibitor(SSRI) fluoxetine;Prozac

(2) Medical therapy - placebo

(3) Physical therapy – Maxillary,hard acrylic stabilisation appliance (splint)

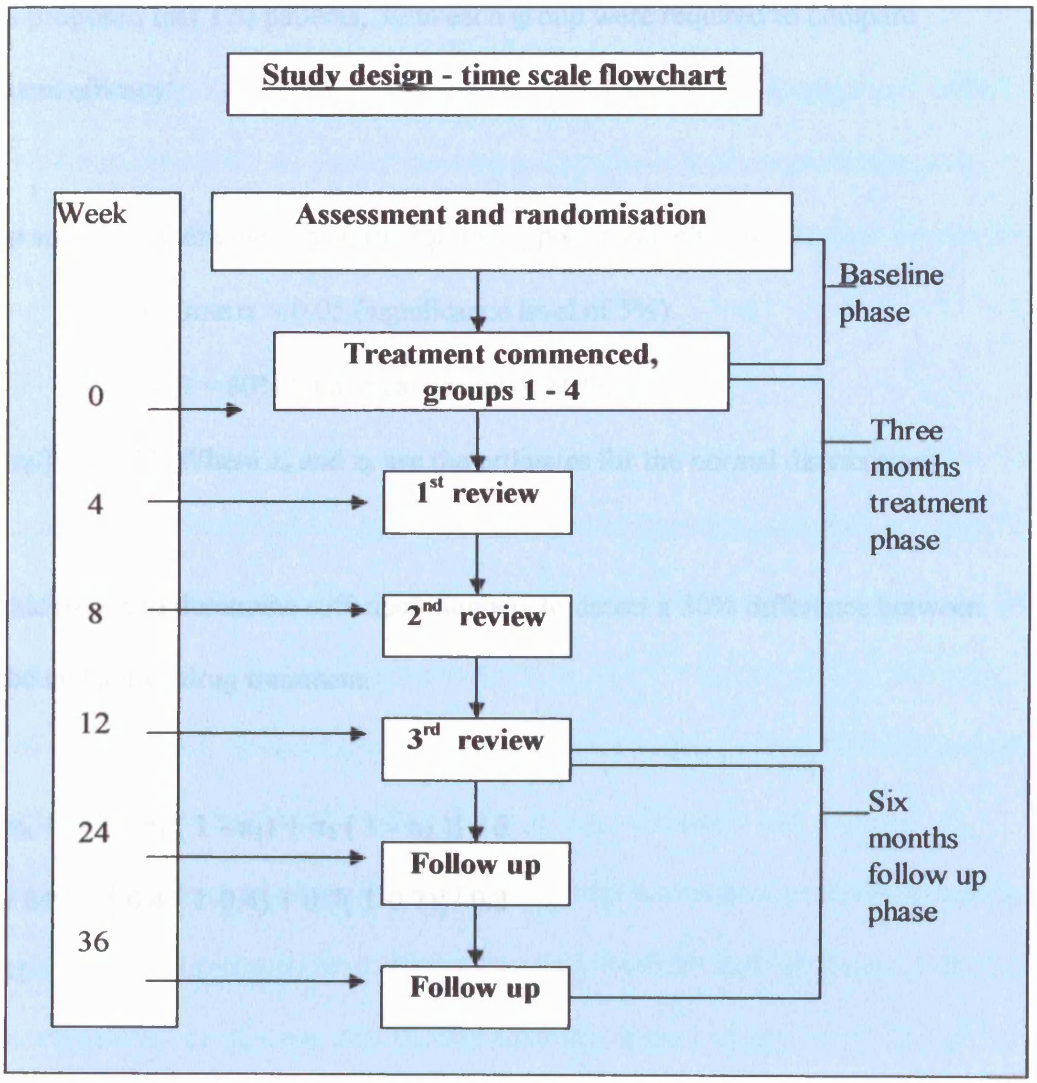
(4) Combined medical and physical therapy – SSRI and splint.

5.2 Study treatment phase

The randomised treatment phase of the study was three months with subsequent follow-up appointments at six and nine months. During the three months trial period monthly review appointments were arranged to assess and monitor progress.

Results of treatment uptake and retention in the trial were analysed for regular interim reporting. The epidemiological characteristics of the referral cohort were described during the trial. However, analysis of treatment outcome was not investigated until closure of the research programme.

Figure 8a:


Study design - time scale flowchart
Week
Assessment and randomisation
Baseline phase
Treatment commenced, groups 1 - 4
0
4
1st review
8
2nd review
12
3rd review
Three months treatment phase
24
Follow up
36
Follow up
Six months follow up phase

5.3 Required sample size and power calculation

It was proposed that 120 patients, 30 in each group were required to compare treatment efficacy.

Group size was determined using the following power calculation: -

Assume $\alpha = 0.05$ (significance level of 5%)

$1 - \beta = 80\%$ (statistical power of 80%)

$(z_\alpha + z_\beta) = 6.172$ (Where z_α and z_β are the ordinates for the normal distribution)

The calculation to determine sufficient numbers to detect a 30% difference between placebo and active drug treatment.

$$m = (z_\alpha + z_\beta) \{ \pi_1 (1 - \pi_1) + \pi_2 (1 - \pi_2)\} / \delta$$

$$= 7.849 \quad \{ 0.4 (1-0.4) + 0.7(1-0.7)\}/ 0.3$$

$$= 31$$

Thus at least 30 patients were required per group for 80% power at 5% significance level. This allowed the presence of potential interaction between treatments in the combined therapy groups.

5.4 Study location and personnel

5.4.1 Site of investigation

The investigation was based in the Oral and Maxillofacial Surgery Department at the Eastman Dental Hospital. All patient assessment, treatment and administration was conducted on site. All record forms, computerised database and medication were stored on site in a locked office .

5.4.2 Research workers

The author was the principal investigator working in conjunction with the lecturer in the Department of Conservation, Mr. Paul O'Neill who dealt with occlusal impressions, fitting and adjustment of the splint and occlusal queries.

The author undertook overall management of the study, supervision and co-ordination of auxiliary clinical, nursing and clerical staff. Screening, assessment and required investigation of all new patients, discussion of alternative treatment or treatment on the study, consent and appropriate correspondence with the GDP and GP. Medical therapy in the three treatment groups was also the responsibility of the author.

A dental nurse and research assistant were responsible for the random allocation and recording of the patients to the four respective groups, data input, collection and scoring of questionnaires and patient appointments.

Statistical advice was sought from the Eastman Dental Hospital

The study was supervised by Dr. Charlotte Feinmann, Mr Richard Ibbetson

and Prof. Malcolm Harris

5.5 Financial Support

Medication was generously donated by Lilly Pharmaceutical Company. The project was funded by a Department of Health Grant and Locally Organised Research funding.

5.6 Ethical aspects

Approval for the project was obtained from the Ethics Committee at the Eastman Dental Hospital, JREC application number:79384.

Informed, signed consent was obtained from all patients who agreed to participate in the study. This was witnessed and signed by both the interviewer (the author) and an observer (the dental nurse). (Appendix 1)

The information received prior to consent was both verbal and written. (Appendix 2)

The possibility of side effects most commonly encountered when taking medication was made known to the patients.

The patients Dental and Medical Practitioner were informed of the patients participation in the study to enable the doctor to have the opportunity to inform the author if there was any extenuating circumstances which should exclude the patient from the study. (Appendix 3)

5.7 Subject selection

In selection of patients it was our intention to preclude long standing chronic pain patients often seen as tertiary referrals within the hospital departments. The intention was to recruit patients who had developed chronic TMD of recent onset, more than three months duration, hence exposed to minimal treatment intervention. New referrals from outside dental practitioners were therefore most suited to this particular study.

5.8 Source of referrals

In January 1995, letters were sent to all the Heads of Department within the Eastman Dental Hospital requesting new patient referrals corresponding to a series of specified criteria. The response from within the hospital was minimal as anticipated due partly to concurrent facial pain projects already in progress and utilising the majority of new patient referrals.

The strategy adopted was therefore to send letters directly to 1,730 GDP's within the London area requesting referral of patients whom they felt may be suitable, would be interested and hopefully benefit from treatment within our study. Letter (Appendix 4)

The initial response was excellent and on average 15 patients were referred per week. A reminder letter was sent out in April to participating GDP's to maintain the good response. A further letter thanking GDP's for their referrals to date and requesting further patients was undertaken. In addition a questionnaire to assess satisfaction with the service provided was issued in January,1997.

5.9 Criteria for participant eligibility

5.9.1 Inclusion criteria

Patients suitable for inclusion were those who presented with diagnostic findings consistent with chronic TMD.This entailed: pain in one or both TMJ's with or without; clicking, limited mouth opening or tenderness in the associated musculature. In addition it was necessary for the patient to present with sufficient teeth for construction of an upper occlusal, hard acrylic splint. The patients may be dentate or partially dentate but with at least two or three clinically sound molars in the maxillary and mandibular arches.

5.9.2 Exclusion criteria

Patients unsuitable for inclusion were those: -

- with inadequate plaque control, extensive or active periodontal disease.
- with active caries.
- undergoing extensive or complex restorative treatment.

  In the prescence of active dental pathology the use of occlusal appliances would be inappropriate. Usage may aggrevate concurrent dental disease especially when oral hygiene is not optimal.
- aged below 16 or over 55 years old.

The lower age limit was to ensure patients were able to consent to treatment. The upper age limit was to preclude the likely condition of osteoarthrosis which tends to be more frequently observed over the age of fifty five years.

- pain for less than three months

TMJ pain of short duration, less than three months, would indicate acute not chronic TMD and does not fit the diagnostic classification for this study.

- history of a joint condition which appears long and intractable

TMJ osteoarthritic pathology or longstanding TMD already treated unsuccessfully by occlusal appliances and antidepressant medical therapies were not included but more appropriate referrals arranged to accommodate these patients' needs.

- patients currently prescribed antidepressant medication
- adverse medical history contraindicating the prescribing of antidepressant medication

  To avoid any potential drug interactions.

5.10 Planned assessment procedure

The measurement of pain is complex, as previously discussed (Chapter 1). Individual suffering and pain perception is virtually impossible to quantify due to broad subjective interpretation. However, it is best accomplished in chronic pain studies, by focusing on functional progress and outcome of therapy, by means of a series of validated self-report questionnaires.

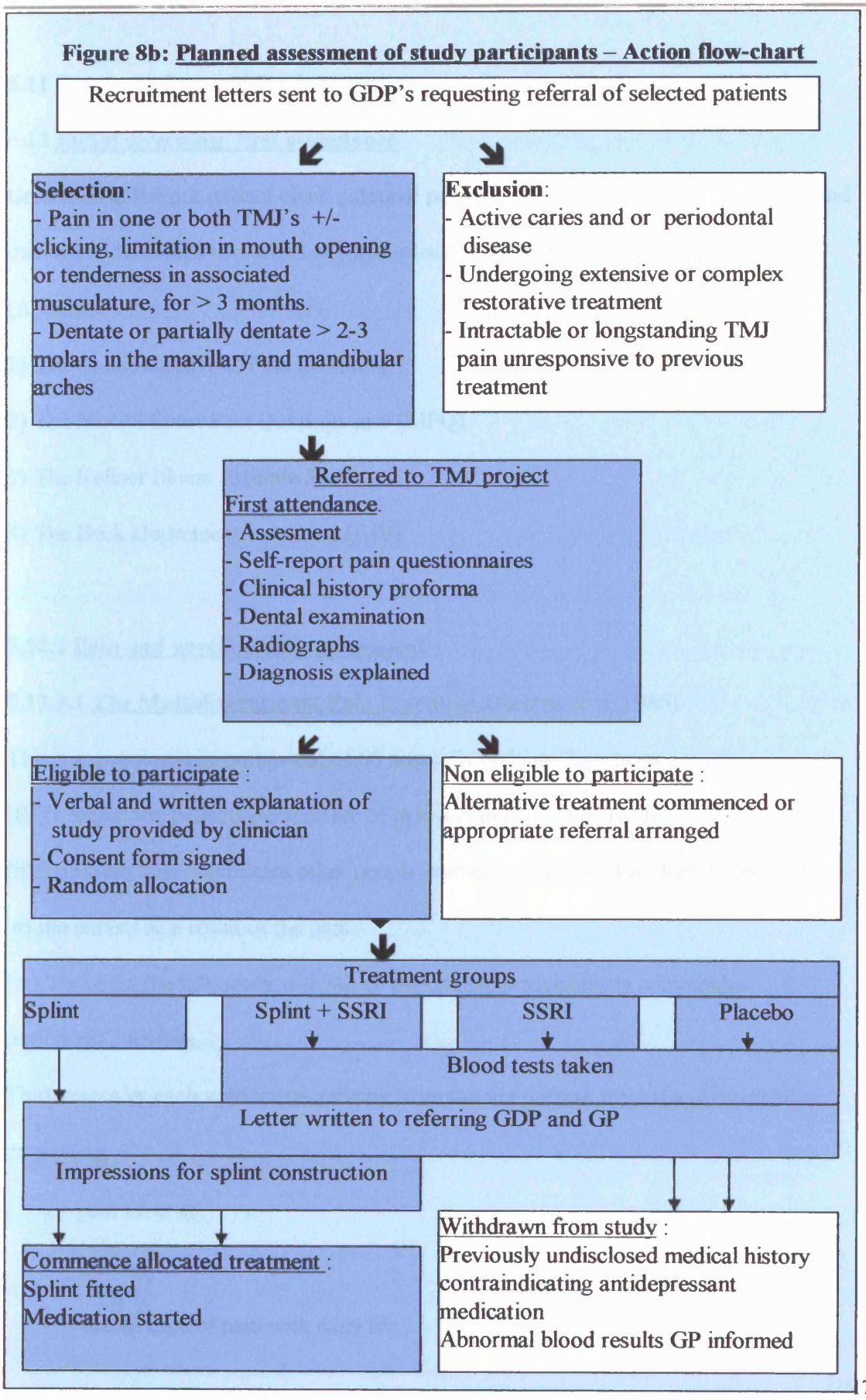
From the literature review of TMD classification (Chapter 2) it was apparent that this well documented chronic pain condition is most appropriately assessed by analysing the intergral biophysical and psychosocial components of the pain experience.

To embrace the biopsychosocial model of pain, assessment and analysis focus on the two integrated components of TMD classification highlighted in the literature.

(a) Clinical examination and history

(b) Pain and psychological questionnaires

Figure 8b: Planned assessment of study participants – Action flow-chart



5.11 Study conduct and implementation

5.12 Initial screening- first attendance

On arrival at the out patient clinic potential participants in the study were registered and then asked to complete a series of standardised self-report pain questionnaires (Appendix 7)

1) The Multidimensional Pain Inventory.

2) The McGill Short Pain Questionnaire (MPQ)

3) The Kellner Illness Attitude Scale

4) The Beck Depression Inventory (BDI)

5.12.1 Pain and psychometric assessment

5.12.1.1 The Multidimensional Pain Inventory (Kearns et al, 1985)

This is a questionnaire comprised of 66 items divided into 3 sections.

(I) To assess the patients perspective of pain and impact on daily life.

(ii) To assess how 'significant other people' namely spouse or close friends respond to the patient as a result of the pain.

(iii) To assess the frequency with which the patient participates in commonly performed activities.

Thirteen scales each with scores ranging from 0-6 are derived from the questionnaire measuring;

- pain severity
- distress
- interference of pain with daily life

- control over one's own life and pain
- response of significant other: support, punishing, solicitous or distracting.
- effect upon ability to : do household chores

  outdoor work

  activities away from home

  social activities

  general activities

5.12.1.2 Short McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987)

This is a modified version of the original long- form McGill Pain Questionnaire (LF-MPQ) described by (Melzack, 1975.) The SF- MPQ measures the subjective quality and intensity of pain using 15 descriptive terms for pain.

Descriptors 1-11 represent sensory dimensions.

Descriptors 12-15 represent affective dimensions

Each descriptor is rated on an intensity scale of 0 - 3,

0= none, 1= mild, 2= moderate and 3= severe.

Three pain scores are derived, the sum of the (a) sensory (b) affective (c) total intensity rank value of the words chosen. The summed score ranges from 0 to 45 and a % is used to represent the patient's usual pain. This ensures a representative score is achieved proportional to the questions answered as opposed to an absolute score, which makes allowance for missing data.

Present pain intensity (PPI)

This intensity rating scale, also found in the LF-MPQ, categorises current pain on a scale of 0-5.

0=no pain, 1=mild, 2=discomforting, 3= distressing, 4=horrible, 5= excruciating.

Visual analogue scale (VAS)

Introduced by Scott and Hutchinson 1976,this consists of a 10cm line used to assess present pain intensity. The line represents a pictorial scale of no pain at one end to unbearable pain at the opposing end.

Both the VAS and PPI describe intensity of pain but not quality of pain.

5.12.1.3 Kellner Illness attitude scale (Kellner, 1981)

The questions relate to the patients understanding of illness and false beliefs in having a disease and fear of a disease. Scores range from 0 to 6, The higher the score the stronger the hypochondriacal and disease phobia beliefs.

5.12.1.4 The Beck Depression Index (Beck et al, 1978)

Originally designed to measure severity of depression in a psychiatric population it is a useful means of assessing patient's mood and level of depression. The 21-item scale contains affective, cognitive, somatic and behavioural items, scored 0-3 with a maximum score of 63.

Scores 0 -9 are classified as not depressed

10 -14 borderline depression

15 -20 mild depression

All questionnaires were completed by the patient prior to being seen for assessment by the clinician. It was explained to the patient this was a method of pain assessment to help us understand the patient's pain and that all information given was confidential.
A cursory check was made to ensure all questions were completed in full and BDI calculated to ensure patients were not suffering from severe depression.

5.12.2 Diagnostic assessment

All patients were seen by the author in the Oral and Maxillofacial surgery department at the Eastman Dental Hospital at the initial consultation. A full pain, dental, medical and social history were obtained from the patient. Physical examination of the head and neck was undertaken, extra oral and intra oral.
All details were recorded on the EDH pain proforma. (Appendix 6) and later transcribed to the Hospital notes.
Radiographs were taken. A standard orthopantomograph (OPG) was taken for all patients to screen for gross pathology. The presence of partially erupted or unerupted wisdom teeth was noted.
Additional radiographs were only taken if indicated by clinical signs and symptoms.
Occipitomental (OM) views - to exclude sinus pathology or fractured zygoma.
Periapical views - to exclude specific dental pathology; caries, periodontal disease, periapical infection or cracked tooth.
Posterior-anterior and Lateral oblique - to exclude a fractured mandible.
Planmeca open and closed view -for suspected unilateral closed lock of the TMJ
Transpharyngeal radiographs (Tome's view) - for suspected dislocation of the mandible

Assimilating the information gained at the consultation, a diagnosis was made.

5.12.3 Diagnostic Criteria

A diagnosis of Temporomandibular joint dysfunction was determined by history, physical and radiographic examination. Described as a preauricular dull ache or discomfort constant or intermittent with or with out occasional sharp episodes. The patient may also experience other symptoms such as clicking or sticking in the joint, difficulty opening the mouth and pain in the jaw muscles extending up into the head and down into the neck. Ear symptoms such as a sense of fullness, popping, buzzing and dizziness may also occur. Diagnosis was explained to the patient and standard reassurance and conservative advice given.

5.12.4 Study exclusion criteria

The exclusion criteria included:-

1. Unsuitable presentation of TMJ symptoms. Frequent clicking of the TMJ was evident but no pain or tenderness.
2. Mildness of symptoms or significant reduction or resolution of symptoms since referral. In these cases explanation of the diagnosis and conservative advice were all that were required to reassure the patient.
3. Incorrect original diagnosis of pain eg. atypical odontalgia, cracked tooth syndrome, migranous neuralgia, temporal arteritis, trigeminal neuralgia, pain of dental origin; caries, periodontal disease and pericoronitis.
4. Inadequate teeth for construction of a splint

5. Adverse medical history or current medication, which contraindicated the prescribing of fluoxetine.

6. Difficulty in travelling to appointments

7. Time commitment in attending appointments and or occasionally lack of patient interest.

8. Reluctance or refusal of patients to consider taking antidepressant medication.

9. Inappropriate age, below 16 years or above 55 years.

10. Significant psychological disturbance or substance abuse.

5.12.5 Alternative treatment for those excluded from the study

Mild cases were given conservative advice and discharged to the continuing care of the GDP. Instructions on bite guard construction and follow up regimes were often sent to the GDP. Any patient suitable but unwilling to participate in the study was not included in the trial series but was treated either with splint therapy by the GDP or medical therapy within the Oral and Maxillofacial surgery department. A significant number of patients were allocated to be participants for the pain management programme with relaxation or self-hypnosis for facial pain, which was undertaken in the department
A small number of patients who had already tried splint therapy were allocated to the project comparing medical therapy versus cognitive behavioural therapy.
In cases were medical therapy and or psychological support are the most appropriate forms of treatment a small number of patients have been maintained on the facial pain clinics under the care of Prof. Malcolm Harris and Dr. Charlotte Feinmann.

5.12.6 Patient Consent

For those allocated to the study, the nature of the investigation was explained verbally with opportunity for the patient to ask questions. An information sheet was also provided for the patient to read and to keep (Appendix 2)

A written consent was obtained from those who agreed to participate.(Appendix 1)

The methods employed in acquiring consent were in accordance with both the MRC guidelines and the Helsinki Declaration, which indicate potential subjects should be informed of the aims, methods, anticipated benefits and potential hazards of treatment and must be at liberty to abstain from the project at any time.

The patients general dental and medical practitioners were informed by a detailed letter of the patients condition and explained that the patient had kindly agreed to take part in the study and that consequently it was proposed to include the patient in a clinical trial. Details of the study were included. (Appendix 3)

5.12.7 Sampling- Patient selection

Patients with the correct diagnosis, who fit the selection criteria and who consented to participate in the study were randomly allocated to one of four groups. Patients were assessed at monthly intervals during the three months treatment period and subsequently at further three-month intervals up to nine months. Additional or alternative treatment were given as deemed appropriate during the nine month follow up period.

5.12.8 Allocation

Patients were randomly allocated to one of four groups, using the method of block randomisation. Randomisation was undertaken by a third party, namely a member of the administration or dental nursing staff. A sealed envelope was opened indicating group participation and recorded in a locked register. The participating patient and clinician were informed whether the patient was to be prescribed medication, splint or combination therapy. Medical therapy was double-blinded so neither patient nor clinician administering interventive treatment and assessing outcome were aware of the assigned treatment.

For those who were to receive medication a blood test was performed at this juncture to check FBC (full blood count), Hb (haemaglobin), LFT (liver function tests), U&E's (urea and electrolytes) and RhF (rheumatoid factor)

For those allocated to the splint group an appointment was arranged for impressions, wax bite and face bow recordings with the Restorative lecturer. The work was then sent to Kurban Dental laboratories for construction of a Michigan splint.

During treatment within the study patients were requested to only embark on minimal essential dental treatment and to refrain from alternative pain therapies.

5.13 Treatment Groups

5.13.1 Physical therapy (Michigan splint)

Details of construction and adjustment (Appendix 10)

5.13.2 Medical therapy (fluoxetine or placebo)

Double blind medical therapy- The clinical investigators and patients involved in the study were blind to medical therapy allocation of drug or placebo. Drugs were coded A or B and the codes for unblinding were held by the Pharmacy Department at the Middlesex Hospital and with a third party at the Eastman Dental Hospital, a supervisor and an administrator, in case of an emergency.

Identical green capsules, in appearance and taste, contained either the medication, fluoxetine, 20mg or placebo. These were provided by Eli Lilly, Belgium. The drugs were packaged by the Middlesex Hospital, UCLH, pharmacy packaging department in identical brown glass bottles with childproof lids. Twenty-eight capsules were contained in each bottle. The later were labelled with the words 'Facial Arthromyalgia (TMJD) study' with the name and address of the hospital, a code number and expiry date.

The correct drugs were selected by the research nurse from the locked drugs proof cabinet. The patient's name, hospital number, the days date and number of tablets to be taken daily were hand written on the bottle and the expiry date checked before handing to the patient at the end of the review appointment.

5.13.3 Combined medical and physical therapy

Patients in this group received both a Michigan splint and Fluoxetine medication.

5.14 Progress and monitoring of treatment

All patients were reviewed at 1 month intervals for 3 months and then 3 monthly intervals up to 9 months. At each 3 month visit a series of questionnaires; an interview and examination were undertaken.

- The self-report pain questionnaires were completed by the patient (Appendix 7)

- A follow up form was completed by the clinician at one-month intervals and three-month intervals. (Appendix 9)

This included severity, frequency, character of pain, current site and distribution, recent emotional disturbance and associated stress related complaints. A clinical examination to assess tenderness to palpation, TMJ noise and interincisal mouth opening were recorded.

- A separate form was also completed at the five review appointments for medical or physical therapy (Appendix 9)

Notes were recorded of splint comfort, compliance of wear and required adjustments. Alternatively or in addition medical compliance, side effects and dosage were recorded. The dosage was doubled from 20mg to 40 mg at the two month review appointment.

Figure 9a :Medication bottles and capsules provided forpatients in groups 1,2& 4.

Figure 9b : **Flat plane stabilization appliance provided for patients in groups 3 and 4.**

Figure 10: Appointments planned for each treatment group

Group	Assessment and randomisation	Week 0	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 24	Week 36
Splint	✸ ✓	I		S		R1	R2	✸R3	✸F6	✸F9
Splint and SSRI	✸ ✓ ●	I M		S		R1	R2	✸R3	✸F6	✸F9
SSRI	✸ ✓ ●	M				R1	R2	✸R3	✸F6	✸F9
Placebo	✸ ✓ ●	M				R1	R2	✸R3	✸F6	✸F9

Key:

✸ Self-report pain questionnaires completed by patient.

✓ Clinical assessment, history, examination, radiographs and correspondence with GP and GDP.

● Blood tests

M Review blood results and start medication

I Impressions and interocclusal records

S Fit splint

R Review appointments, during trial phase (**R1**- 1 month, **R2**- 2 months, **R3**- 3 months)

F Follow up appointments (**F6**- 6 months, **F9**- 9 months)

Figure 11: Treatment of Study participants – Action flow chart				
Week	**Medication (SSRI)**	**Placebo**	**Medication (SSRI) and splint**	**Splint**
Assessment	Assessment and random allocation to one of the four groups			
	Blood test			
0	Check blood results,start 20mg capsule daily			
			Impressions and interocclusal records	
1				
2			Splint fitted	
3				
4	One month follow up form, review medication, 20mg daily.			
			One month follow up form, review splint.	
5				
6				
7				
8	Two month follow up form, review medication increase to 40mg daily			
			Two month follow up form, review splint	
9				
10				
11				
12	End of trial phase - Review splint and / or medication and modify treatment plan Three month follow up forms and self report questionnaires.			
24	Six month follow up forms and self report pain questionnaires			
36	Nine month follow up forms and self report pain questionnaires			

5.15 Withdrawal criteria

Patients were withdrawn from the study if there was a significant alteration in the patients medical condition or if side effects were deemed intolerable.

5.16 Follow up after the three-month trial

At the conclusion of the three month trial period, patients who had gained benefit from the splint therapy continued usage but discontinued if it had been found non beneficial. Patients who had improved on medical therapy and wished to continue on treatment remained on medication usually at the 40mg dosage. Those where pain had failed to respond to therapy or had worsened were reassessed and in some cases withdrawn from continuation in the study. Further data was however collected from these patients to include in the intention to treat analysis. An alternative antidepressant medication, lofepramine 70mg nocte was prescribed in some cases or referral for surgical management in the form of an arthroscopy for internal derangement of the TMJ and closed lock.

The patient's general medical and dental practitioners were kept informed of their patient's progress and of any further treatment given.

After the three months assessment patients were seen at three monthly intervals to follow the course of their symptoms and to monitor continued treatment requirements. Further questionnaires were completed up until the nine-month trial end point.

5.17 End of trial and management of intractable pain patients

The majority of patients were discharged back to their referring practitioner and letters written accordingly. A small number of patients were maintained on facial pain clinics for

review of symptoms and further treatment.

5.18 Data analysis

SPSS an abbreviation of Statistical Product and Service Solutions (formerly Statistical Packages for the Social Sciences),version 8.0 – 11.01 for windows, was the data base used for all data processing and analysis.

5.19 Statistical methods

Statistical advice was given by John Bullman and David Moles at the Eastman Dental Hospital.

Descriptive statistics were used to examine the clinic population and TMD study cohort. Parametric and non-parametric tests were applied to compare group subsets and treatment efficacy. Recordings at baseline, with repeated measures during the treatment phase and or at the end of the trail period of three months were analysed. Follow up data was also analysed at six months and nine months post therapy.

In addition to the analysis of those competing treatment, intention to treat analyses, for all those originally allocated to treatment and imputation analyses for incomplete data were performed where appropriate and presented separately in graphical and tabular format. Sub group analysis of depressed, initially high pain scores and the characteristics of those who responded to therapy were also noted.

A numbers needed to treat (NNT) analysis was used for the primary outcome measure of greater than 50% pain improvement.

5.19.1 Numbers needed to treat (NNT) analysis

Therapeutic outcome of a specific treatment can be described using the NNT (Lampacis et al,1988, Cook and Sackett,1995, McQuay and Moore,1998).It is a useful summary applicable to clinical practice and indicating the most appropriate choice of treatment.

	Placebo (control)	Active treatment
Total number of patients	N_{cont}	N_{act}
Clinical endpoint, improvement achieved	Imp_{cont}	Imp_{act}

$$NNT = \frac{1}{(Imp_{act} / N_{act}) - (Imp_{cont} / N_{cont})} = \frac{1}{ARR}$$

Where ARR, the absolute risk reduction is the difference between the event rate in the experimental group and the control group.

An NNT of 1 indicates an ideal (100%) benefit where every patient given the treatment has a favourable outcome. This would be the aim of an antibiotic or analgesics in acute pain, although effective treatments are more usually in the range 2-4 and prophylactic treatment 20-40,(Moore,1999).

In this study, the definition for target improvement, as specified in the protocol was >25% pain relief. In the medical literature pain relief is frequently quoted as >50%. Consequently the power calculation for this trial was undertaken with the higher 50% percentage, so that both 50% and 25% pain relief could be investigated.

5.19.2 Statistical analysis for secondary outcome measures

Non parametric statistical analysis was undertaken for categorical, ranked, ordered and dichotomous secondary outcome measures apart from interincisal mouth opening which was clearly an interval scale. Visual analogue scale (VAS) 0-10cm, for recording pain intensity was analysed using both parametric and nonparametric analysis.

Intra group analysis was undertaken using the non-parametric Freidman two-way ANOVA and where significance was indicated Wilcoxons tests performed post hoc. For dichotomous data Cochran and McNemar tests were performed. For parametric data a repeated measures ANOVA was performed with paired sample t-tests between individual time points.

Intergroup analysis, to assess difference in efficacy between treatment groups was performed using the nonparametric Kruskall-Wallis test and if required Mann-Whitney post hoc tests. For dichotomous data Chi squared tests were performed and for parametric interval data one-way ANOVA.

Completers analysis, for those patients who completed the study with no protocol deviations; intention-to-treat analysis, for those individuals who failed to complete initially allocated treatment and imputation analysis (last score brought forward), for those with incomplete data, were performed where appropriate.

Multivariate analysis; logistic regression and discriminant analysis were used to assess individual factors as predictors of outcome.

RESULTS

AND

DISCUSSION

6.0 An overview of the study

6.0.1 Hypotheses

To be derived from the RCT, primary outcome measures- Chapter VII

(1a) An SSRI (fluoxetine;Prozac) in daily oral doses of 20-40mg is more effective than placebo in the treatment of patients with chronic TMD.

(1b) A combination of an SSRI (fluoxetine;Prozac) and a bite guard are more effective than fluoxetine or bite guard alone in the treatment of chronic TMD.

To be derived from the baseline data of the referral study cohort – Chapter VI

(2) The demographic and epidemiological features of the study cohort, are consistent with the patient population seen within a secondary or tertiary TMJ clinic.

(3) The duration, character and location of TMD pain described are typical of a patient population seen within a secondary or tertiary TMJ clinic.

To be derived from the RCT, secondary outcome measures-Chapter VII

(4a) A significant improvement in the 'clinician recorded' intensity, interference and frequency of patient TMD pain, is only observed in the dual therapy group.

(4b) A significant improvement in the 'self recorded' impact of TMD pain on daily life; MPI severity, interference, life control and affective distress is only observed in the dual therapy group.

(4c) There is a significant difference in 'self recorded' BDI depression scores between the commencement and completion of the study.

(4d) There is a significant difference in 'self recorded' Kellner illness attitude and beliefs between commencement and completion of the study.

(5a) There is a significant improvement in the signs and symptoms of TMD between the commencement and completion of the study.

(5b) A significant improvement in the signs and symptoms of TMD are only seen in those wearing a bite guard.

(5c) There is a significant difference in the number of co-morbid pain conditions reported between the commencement and completion of the study.

(5d) A significant improvement in co-morbid pain conditions are only seen in those taking SSRI (fluoxetine).

To be derived from the post hoc subgroup analysis – Chapter VIII

(6a) A significant and measurable improvement in pain is only seen in those patients without depression at baseline

(6b) A significant and measurable improvement in pain measures are only seen in those patients with initially high pain scores

(6c) Clinical and pain history characteristics at baseline separate the treatment responders from the non responders.

To be derived from adherence and adverse events data recorded during the RCT- Chapter IX

(7) The four therapeutic groups were equally adherent to therapy

(8) There was no significant difference in adverse events between active and placebo medication

To be derived from post RCT follow-up analysis- Chapter IX

(9) The improvement in pain measures at the end of the RCT are maintained at six and nine month follow-up.

6.0.2 Summary of Randomised controlled trial (Figure 12)

The reporting of the RCT is illustrated by means of a flow diagram, in accordance with CONSORT (Consolidated statement of reporting trial) guidelines, figure 12. This illustrates the progression of participants through the trial period and subsequent follow-up with completion and drop-out. The figure provides an outline of the numbers involved in enrolment, allocation, follow-up and post treatment follow-up phases, discussed in detail during the course of the results

6.0.3 An overview of the presentation of results

A description of the referral cohort (n=1,038) is first presented with regard to patient source of referral, previous consultations and treatments for TMJ/facial pain. Diagnosis and reasons for exclusion from study participation are reported, with alternative treatment or referral provided. **(6.1)**

The study cohort (n=250) is then examined in detail. Demographic and social characteristics, clinical history and examination and self report questionnaires are presented. Later, in the discussion, these results are compared with previously reported studies, suggesting the data is comparable to a generalised TMD clinic population, **(6.4)**. Inter group analysis of the study cohort is undertaken to ensure true randomisation, showing an even distribution of characteristics between the four treatment groups at baseline,**(6.2).**

The results of the RCT are presented **(7.0),** starting with the primary outcome measure, **(7.1)** NNT analysis, using the VAS, 10cm line, >50% pain improvement. Secondary

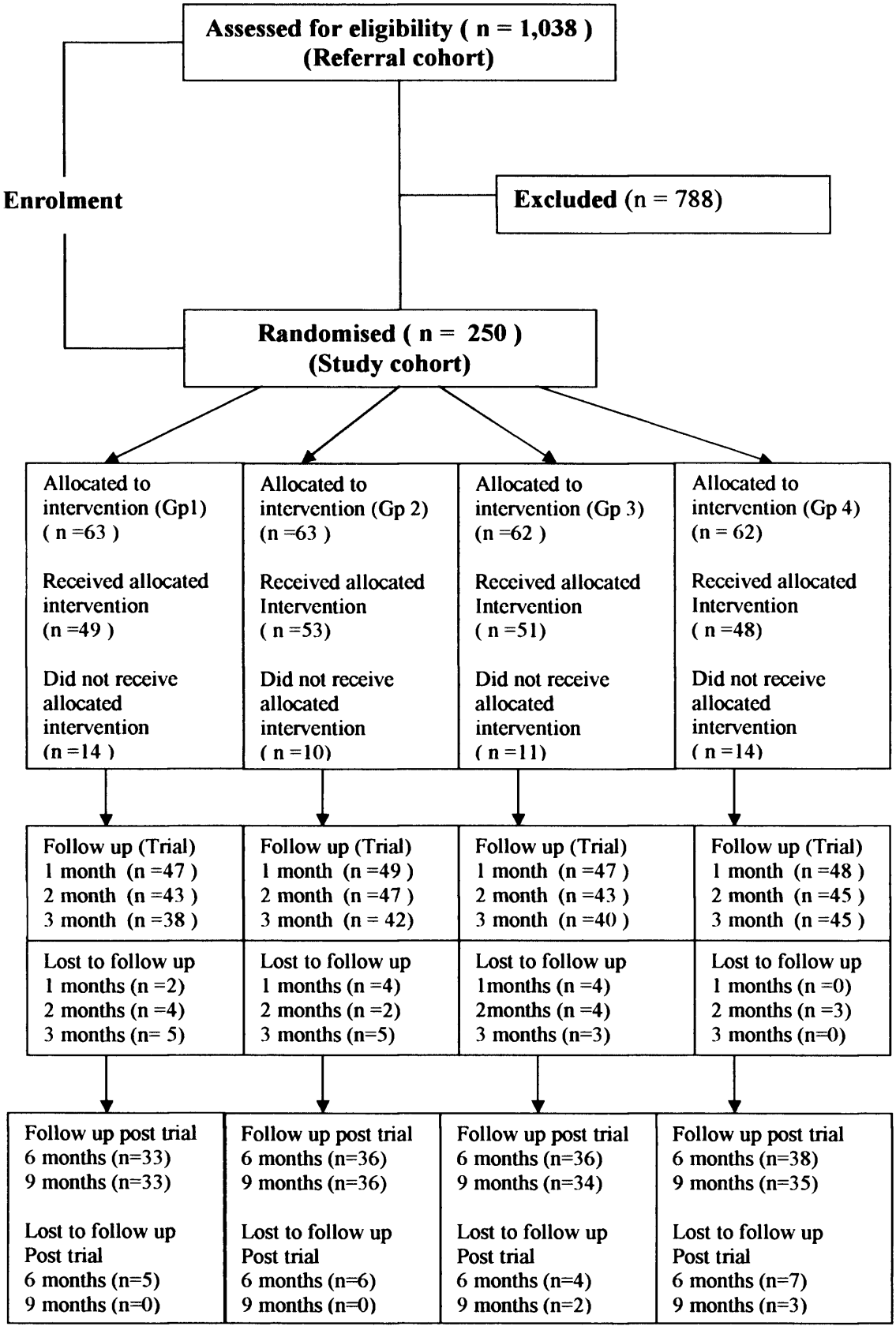
outcome measures are divided into self-reporting verbal rating scales, clinical outcome measures and self report pain questionnaire scores **(7.2)**. PPI, frequency and interference are next presented in tabular and graphical form,**(7.2.1)**. Clinical outcome measures are shown with improvement in signs and symptoms, including interincisal mouth opening, TMJ and associated muscular tenderness **(7.2.2)**
Self report pain questionnaire data is then reported in tabular and graphical format illustrating the difference in scores over the three month treatment period,**(7.2.3)**.
Outcome predictors are investigated using logistic regression analysis, **(7.3)**.

(8.0) Subgroup analysis focuses on three main distinctions: depressed and non depressed **(8.1)**, high and low initial pain scores **(8.2)** and responders and non responders to therapy **(8.3)**.

In the final results section, maintenance and withdrawal from therapy and post treatment follow up are analysed **(9.0)** The adherence or compliance to therapy and any adverse effects of treatment are reported,**(9.1)**.Follow-up data examines the post treatment phase, recorded three and six months from the end of the study phase. An analysis of outcome measures; VAS, PPI, frequency, interference, clinical data and pain questionnaire scores are presented, **(9.2)**.

Finally, having discussed results, theories and conclusions are drawn **(10.0)**.

Figure 12: Flow chart of participants progress through stages of RCT



Flow chart according to the CONSORT guidelines

VI RESULTS

EPIDEMIOLOGY

REFERAL AND STUDY COHORT

6.1.0 THE REFERAL COHORT

Referrals to the Eastman Dental Hospital were accepted over a four year period 1995-1999. During this time; 1,038 subjects, with a potential diagnosis of Facial Arthromyalgia (chronic TMD), were screened and assessed for study eligibility. Recruitment was continued until the planned cohort of 250 patients was achieved.

6.1.1 Demographic data:

The mean age of subjects in the referral cohort was 37 years (+/-SD13),(range 8 – 88 years), with a gender distribution of 1:4 (22% male,78% female).The mean duration of pain on presentation was 3 (+/-SD4.4) years,(range one week -32 years).

6.1.2 Referral source:

The predominant source of referral was General Dental Practitioners (GDPs) 950/1038 (92%) as illustrated in figure 13. This was to be expected following the targeted GDP letters requesting study participants. Other referral sources, included; General Medical Practitioners (GPs) 385/1038 (3%) and Hospital Specialists 58/1038 (6%) from both the medical and dental fields.

6.1.3 Previous patient consultations regarding TMJ/Facial pain:

Illustrated in figure 14, the majority of patients had previously sought the advice of a GDP 962/1038 (93%), consistent with the pattern of referral source. However, 385/1038 (37%) had consulted their GP, 107/1038 (10%) an Oral Surgeon, 92/1038 (9%) ENT surgeon, 33/1038 (3%) Neurologist and 18/1038 (2%) Psychiatrist showing the diversity in clinicians associated within the domain of facial /TMJ pain.

6.1.4 Total number of clinicians seen for consultations regarding facial/TMJ pain:

Most patients had seen either one or two clinicians 546/1038 (53%) and 322/1038 (31%) respectively, as illustrated in figure 15. The maximum number of clinicians seen was 6/1038 (0.1%) whilst 39/1038 (4%) did not recall having previously sought help specifically for facial/TMJ pain, the condition only having been discussed as a secondary complaint during the course of a consultation appointment.

6.1.5 Previous treatment received for Facial/TMJ pain

The aim of the study was to enrole patients with no previous treatment intervention. An enquiry into previous treatment received ranged from conservative, self administered analgesics to invasive, surgical exploration of the TMJ, as illustrated in figure 16.The most popular treatment was the use of analgesics 306/1038 (29%) and occlusal appliances 184/1038 (18%).

6.1.6 Total number of previous treatments per patient for Facial/TMJ pain.

Illustrated in figure 17, (483/1038) 53% of patients had received no previous treatments. (321/1038) 31% had received one and (150/1038) 14% two previous treatments, (83/1038) 8% three to six previous treatments, whilst (1/1038) 0.1% had received over 12 previous treatments.

6.1.7 Diagnoses of referral cohort:

Following history, clinical and radiographic examination not all patients were ascribed a diagnosis of chronic TMD (Facial Arthomyalgia), as illustrated in table 6. 131/1038 (13%) did not have a primary diagnosis of TMD, 907/1038 (87%) did have a diagnosis of TMD. However, 59/907 (7%) of this latter group were classified as mixed diagnoses. In addition to TMD, this included a diagnosis of other chronic idiopathic

orofacial pain 34/907 (4%) or concomitant dental pathology affecting teeth or periodontium 25/907 (3%). 6/907 (0.7%) had acute TMD but 848/907 (68%) had a diagnosis of chronic TMD. Overall, 848/1038 (60%) met the correct diagnostic criteria for study inclusion.

6.1.8 Recruitment from referral cohort

During the enrolment procedure for the study, 788/1038 (76%) were excluded from participation. This was due either to inappropriate diagnosis 131/1038 (13%), indicated above, or due to other exclusion/inclusion criteria as outlined in the methods

6.1.9 Reasons for those diagnosed with TMD not participating in the study.

Reasons for non participation are outlined in table 7. The most commonly occurring exclusion criteria for those diagnosed with TMD were: TMD pain not severe enough to interfere with life or require treatment 125/848 (14.7%), patient not keen to take tablets 124/848 (14.6%), no current TMD pain 78/848 (9.2%) and not enough time to participate in the study or travel difficulties in attending for the study 30/1038 (38%)

6.1.10 Treatment received and referrals made for those patients with TMD

Patients with a diagnosis of TMD, who did not participate in the study, received a range of treatments, table 8. All patients received informed reassurance; explanation of the condition and simple self care management. 274/848 (45.8%) were content with informed reassurance alone. The most frequent, additional treatment 147/848 (24.6%) was referral back to their GDP for a splint. 53/848 (8.9%) were prescribed medication and review arranged, 25/848 (4.2%) were provided with a splint and reviewed. Referrals were made to: the GP 17/484 (2.8%), hospital medical and dental consultant clinics 15/848 (2.5%) or to studies within the department 26/484 (4.3%) for hypnosis and relaxation skills, 4/848 (0.7%) for medical and or cognitive behavioural therapy.

Figure 13: Referral source

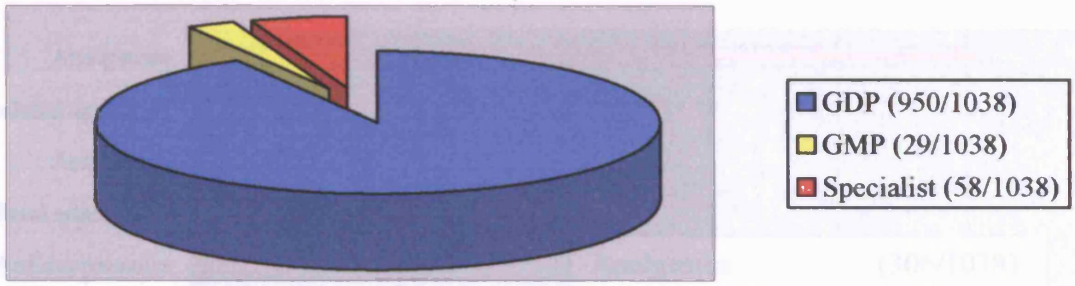


Figure 14: Previous patient consultations regarding Facial / TMJ pain

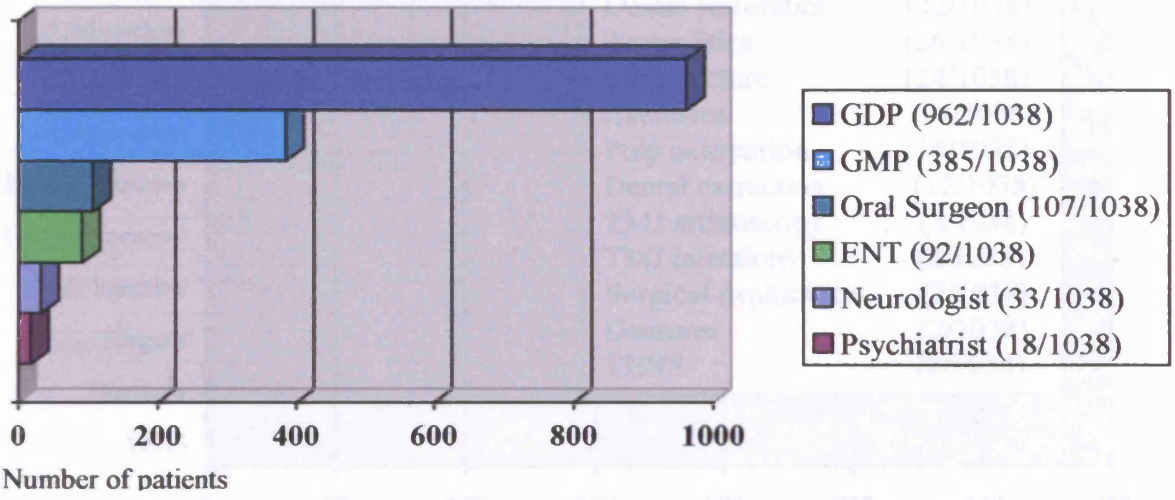


Figure 15: Total number of clinicians seen for consultations regarding facial / TMJ pain

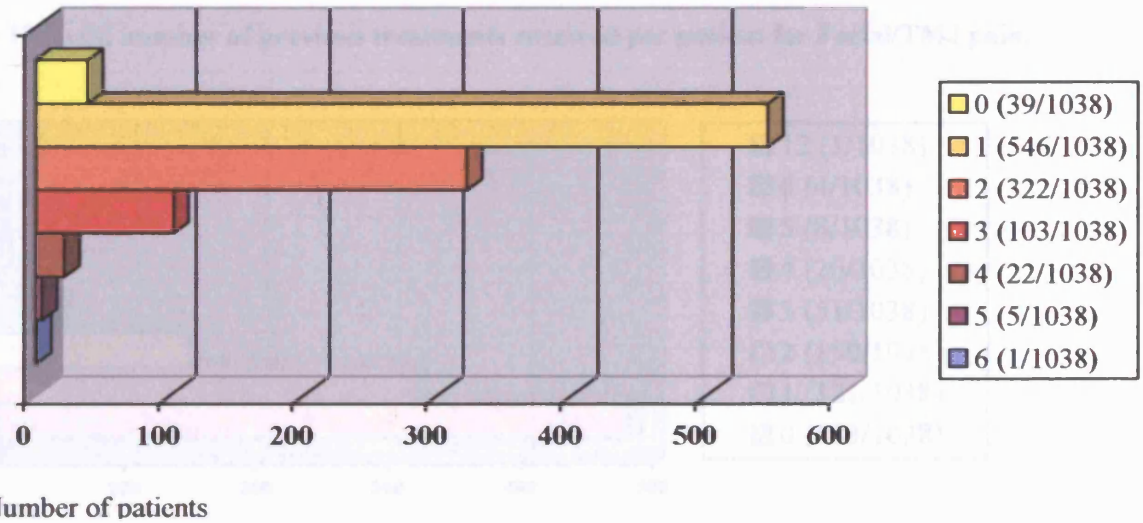


Figure 16: Previous treatment received for Facial/TMJ pain

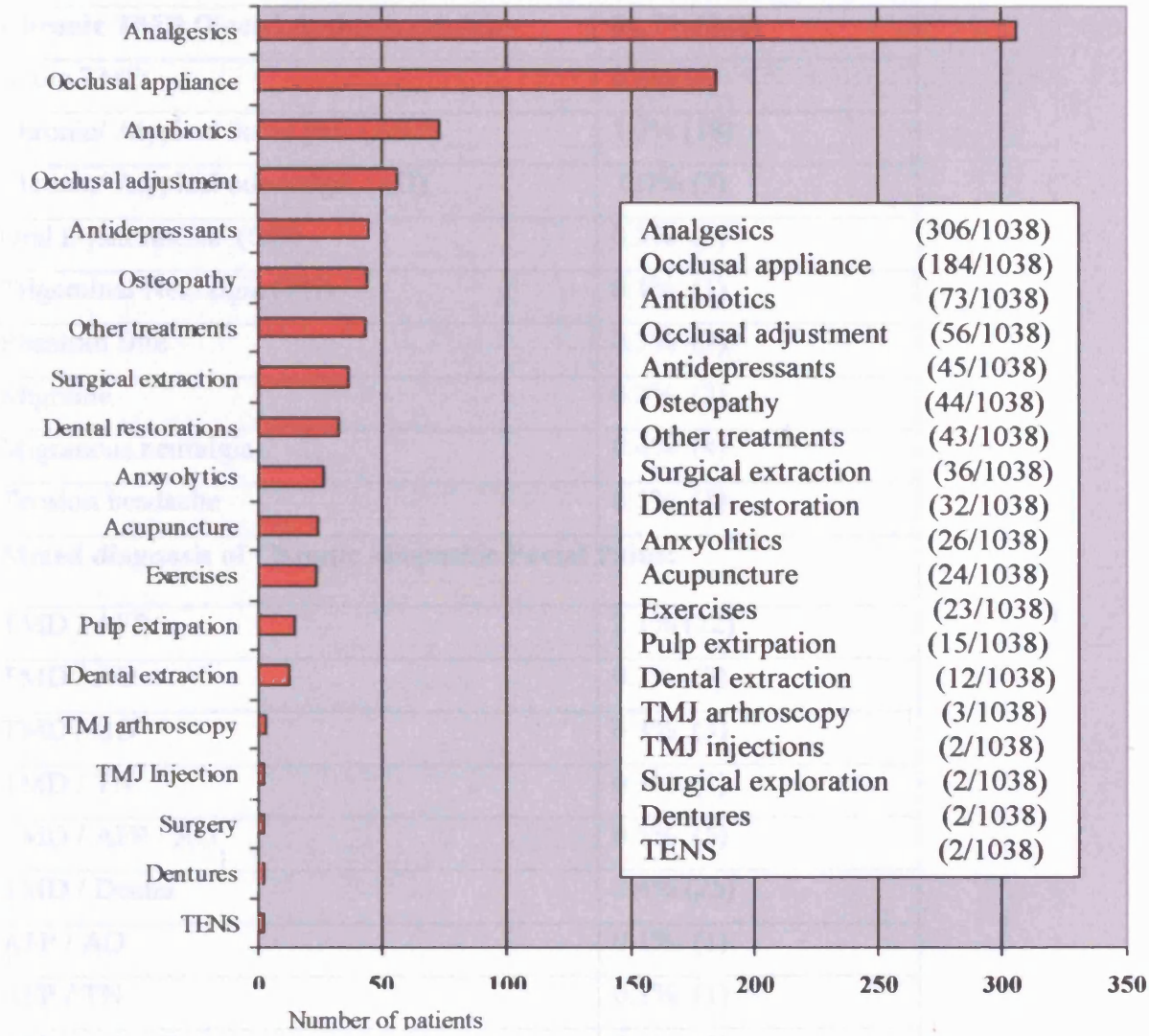


Figure 17:Total number of previous treatments received per patient for Facial/TMJ pain.

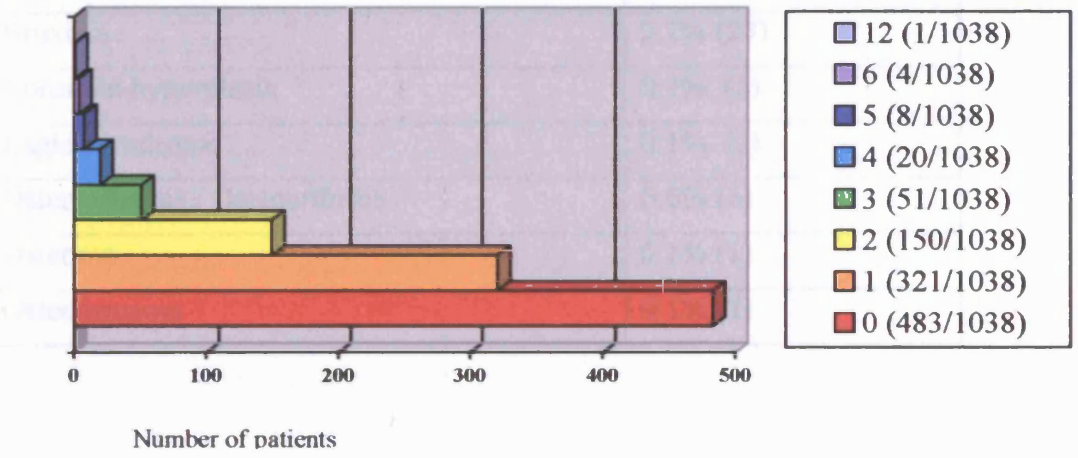


Table 6: Diagnoses of referral cohort (n=1,038) % (number of cases)

Chronic idiopathic Facial Pains:	
Chronic TMD (Facial Arthromyalgia)	**81.7%(848)**
Acute TMD	0.6% (6)
Chronic/ Atypical facial pain (AFP)	1.7% (18)
Chronic/ Atypical odontalgia (AO)	0.7% (7)
Oral Dysaesthesia (OD)	0.3% (3)
Trigeminal Neuralgia (TN)	0.1% (1)
Phantom Bite	0.3% (3)
Migraine	0.3% (3)
Migranous neuralgia	0.4% (4)
Tension headache	0.1% (1)
Mixed diagnosis of Chronic idiopathic Facial Pains:	
TMD / AFP	2.1% (22)
TMD / AO	0.3% (3)
TMD / OD	0.3% (3)
TMD / TN	0.1% (1)
TMD / AFP / AO	0.5% (5)
TMD / Dental	2.4% (25)
AFP / AO	0.1% (1)
AFP / TN	0.1% (1)
AFP / AO / TN	0.1% (1)
Other diagnoses:	
Dental caries / Periodontal disease	4.7% (49)
Bruxism	2.2% (23)
Coronoid hyperplasia	0.1% (1)
Eagles syndrome	0.1% (1)
Osteoarthrosis / Osteoarthritis	0.6% (6)
Osteoma	0.1% (1)
Osteosarcoma	0.1% (1)

Table 7: Reasons for those diagnosed with TMD not participating in the study.

Eligible and consented to participate in the study	**29.5% (250)**
Reasons for non participation	
Not severe enough to interfere with life or require treatment	**14.7% (125)**
Does not want to take tablets	**14.6% (124)**
No pain at present	**9.2% (78)**
Not enough time or travel difficulties	**4.5% (38)**
Reassured, self management	**3.4% (29)**
Age restriction (<16,>55 years)	**3.1% (26)**
Already taken or currently taking fluoxetine (Prozac)	**3.1% (26)**
Already taken or currently taking other antidepressant medication	**2.8% (24)**
Does not want or unsuitable for splint	**2.7% (23)**
Not keen on participating in a study	**2.6% (22)**
Already has or has had splint	**1.9% (16)**
Prefers referral for hypnotherapy and relaxation study,EDH.	**1.4% (12)**
Mental health problems	**1.1% (9)**
English language difficulties	**0.7% (6)**
Medical history exclusion	**0.7% (6)**
Substance abuse	**0.6% (5)**
Dentistry required	**0.6% (5)**
Emigrating or travelling abroad	**0.6% (5)**
Pregnant	**0.4% (3)**
Does not wish to complete questionnaires	**0.4% (3)**
Not keen on the concept of a placebo	**0.4% (3)**
Prefers referral for medical and CBT study,EDH.	**0.4% (3)**
Prefers to try alternative therapy	**0.4% (3)**
To continue with alternative therapy	**0.2% (2)**
Referral to consultant clinic due to severity of symptoms	**0.2% (2)**
TOTAL	**100% (848)**

Table 8: Treatment received and referrals made for those patients with TMD

Randomised TMD study treatment	**29.5% (250)**
Treatment and referrals for those not participating in study.	
Informed reassurance	**45.8% (274)**
Refer to GDP for splint	**24.6% (147)**
Medication prescribed and review arranged	**8.9% (53)**
Refer to Psychologist, Hypnosis / Relaxation therapy study.	**4.3% (26)**
Splint provided and review arranged	**4.2% (25)**
Refer to GP	**2.8% (17)**
Refer to Hospital Consultant clinics: Maxillofacial and Oral Surgery, Dental Specialties, Neurology, Rheumatology, ENT, Psychiatry, Clinical Psychology, Interdisciplinary joint pain clinic,	**2.5% (15)**
Refer to CBT / Medical therapy study.	**0.7% (4)**
TOTAL	**100% (848)**

6.2 THE STUDY COHORT

6.2.1 DEMOGRAPHIC CHARACTERISTICS

6.2.0 THE RESEARCH STUDY, TREATMENT COHORT

250 patients were eligible and consented to participate in the research study.
The sample characteristics of those patients selected for the study were analysed to assess demographic and social details, pain, dental and medical histories, clinical findings and patient response to the MPI, MPQ, Kellner and Beck depression indices.
The demographic and social details (6.2.1), clinical history (6.2.2), clinical examination (6.2.3) and self-report questionnaires (6.2.4) are analysed to determine the overall characteristics of the study cohort and to ensure true randomisation had been achieved amongst all four treatment groups, prior to commencing analysis of the outcome data.

6.2.1 Demographic characteristics of TMD study cohort

Patients within the research study were predominantly female, 76% (191/250), compared to male, 24% (59/250), (fig.20). Age was a mean 32.3yrs (SD 9.58) (range 16 –55), males ,mean 32.2 yrs (SD 9.72), females, mean 32.3yrs (SD 9.55),(fig.19).
The majority of patients were employed 167/250 (66.8%), (fig.22) in socioeconomic group II (semi professional) and group IIIi (non professional clerical) 144/250 (57.6%), (fig.21). In table 9, gender was compared, showing significant variation in socioeconomic status (p=0.002), employment status (p=0.021) and referral source (p=0.046).
Treatment categories were then compared to ensure an even distribution of individuals between groups. Demographic details of each group are compared in table 10.Age, gender, marital status, socio-economic status, employment status, referral source and duration of pain were not significantly different between the four treatment groups.
Subjects within the study cohort were predominantly female (76%), employed (66.8%), in the third decade of life, having experienced pain for a mean three years, (fig.18).

Figure 18: Duration of TMD pain

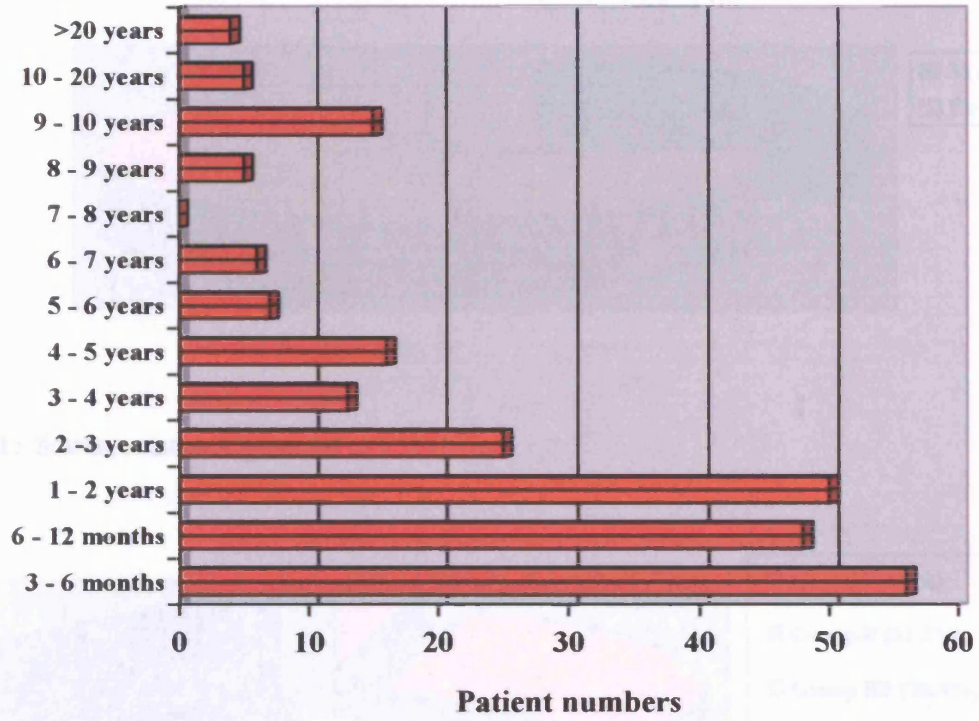


Figure 19: Age Distribution

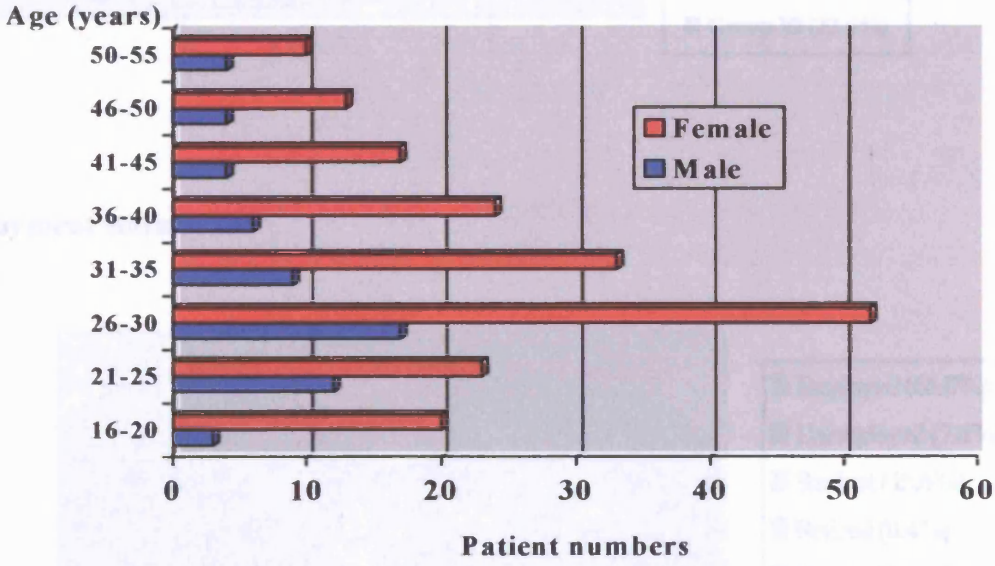


Figure 20: Gender distribution

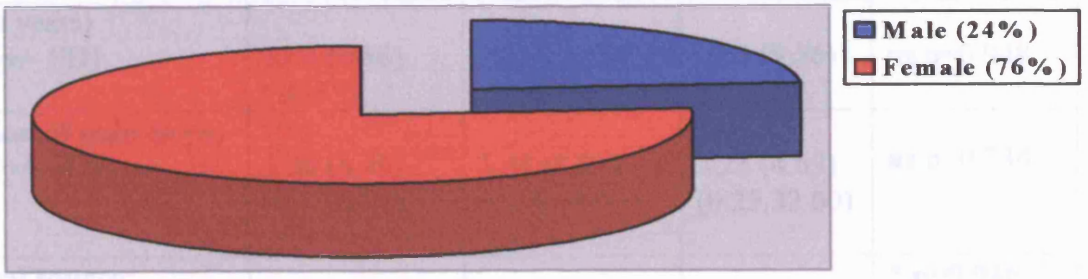


Figure 21: Socioeconomic groups

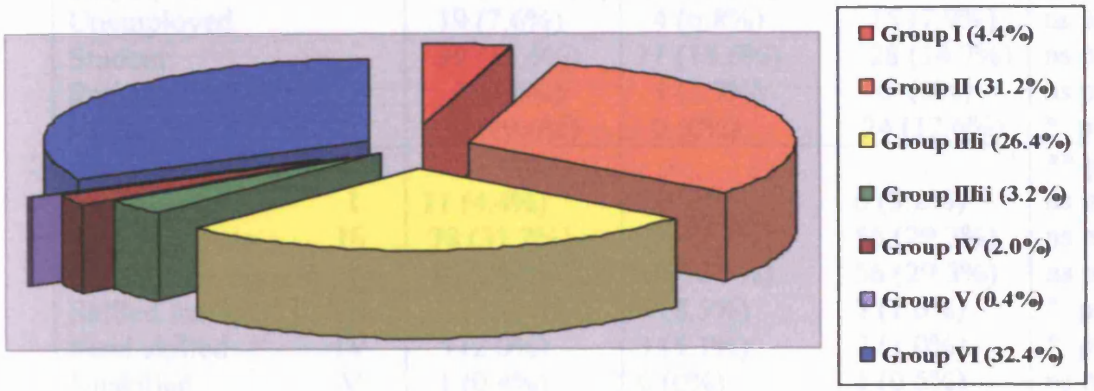


Figure 22: Employment status

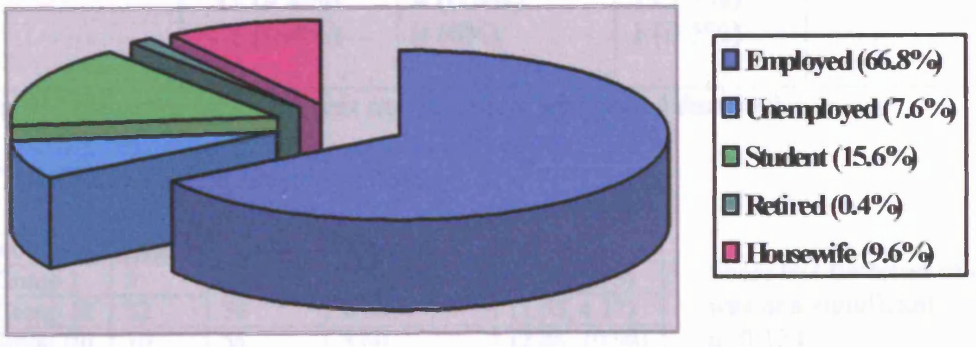


Table 9 : Demographic details of study cohort, comparing gender (n=250)

Recorded at baseline assessment	All groups (n=250)	**Male** (n=59)	**Female** (n=191)	Significance between gender
Age (in years)				
Mean (+/- SD)	32.3 (9.58)	32.2 (9.72)	32.3 (9.56)	**ns** p=0.948
Range	(16-55)	(16-53)	(15-55)	
Duration of pain (in yrs)				
Mean (+/- SD)	3.30 (4.49)	3.48 (3.91)	3.25 (4.67)	**ns** p=0.734
Range	(0.25-32.0)	(0.25,18.00)	(0.25,32.00)	
Referral source				*** p=0.046**
GDP	230 (92.0%)	50 (84.7%)	180 (94.2%)	* p=0.019
GP	6 (2.4%)	2 (3.4%)	4 (2.1%)	ns p=0.570
Specialist	14 (5.6%)	7 (11.9%)	7 (3.7%)	ns p=0.170
Employment status				*** p=0.021**
Employed	167 (66.8%)	43 (72.9%)	124 (64.9%)	ns p=0.256
Unemployed	19 (7.6%)	4 (6.8%)	15 (7.9%)	ns p=0.786
Student	39 (15.6%)	11 (18.6%)	28 (14.7%)	ns p=0.461
Retired (medical)	1 (0.4%)	1 (1.7%)	0 (0%)	ns p=0.071
House wife	24 (9.6%)	0 (0%)	24 (12.6%)	* p=0.004
Socio-economic status				**** p=0.002**
Professional I	11 (4.4%)	5 (8.5%)	6 (3.2%)	ns p=0.081
Intermmediate IIi	78 (31.2%)	22(37.3%)	56 (29.3%)	ns p=0.248
Skilled non-manual IIii	66 (26.4%)	10(16.9%)	56 (29.3%)	ns p=0.060
Skilled manual III	8 (3.2%)	5 (8.5%)	3 (1.6%)	* p=0.008
Semi skilled IV	5 (2.0%)	3 (5.1%)	2 (1.0%)	* p=0.053
Unskilled V	1 (0.4%)	0 (0%)	1 (0.5%)	ns p=0.578
Unemployed, house wife, student, retired VI	81 (32.4%)	14 (23.7%)	67 (35.1%)	ns p=0.103
Marital status				**ns** p=0.375
Single	147 (58.8%)	39 (66.1%)	108 (56.5%)	
Married	89 (35.6%)	15 (25.4%)	74 (38.7%)	
Seperated	2 (0.8%)	1 (1.7%)	1 (0.5%)	
Divorced	11 (4.4%)	4 (6.8%)	7 (3.7%)	
Widowed	1 (0.4%)	0 (0%)	1 (0.5%)	

Significance test, Chi-squared (Independent samples t-test for age and duration).

Table 9a: Trends in socio-economic groups.

Socio-economic status	Male	Female	Odds ratio	95% CI
Group I	5	6	1.20	(0.37, 3.93)
Group IIi	22	56	2.55	(1.55, 4.17)
Group IIii	10	56	5.60	(2.86, 10.98)
Group III	5	3	0.60	(0.14, 2.51)
Group IV	3	2	0.67	(0.11, 3.99)
Group V	0	1	-	-
Group VI	14	67	4.79	(2.69, 8.51)

Score test for trend of odds was non significant p=0.124

Table 10: Demographic details of study cohort, comparing treatment groups. (n=250)

Recorded at baseline assessment	**Group 1 (n=63)**	**Group 2 (n=63)**	**Group 3 (n=62)**	**Group 4 (n=62)**	Significance between groups
Age (in years) Mean (+/- SD) Range	29.8(7.99) (16-55)	32.8 (10.0) (16-54)	32.6 (9.85) (17-54)	34.1(9.99) (16-55)	**ns** p=0.076
Duration of pain (in yrs) Mean (+/- SD) Range	3.04 (4.68) (0.25-32)	2.99(3.64) (0.25-22)	3.86(4.65) (0.25-25)	3.31 (4.96) (0.25-30)	**ns** p=0.692
Gender M: F	2.4 : 7.6 23.8% (15) 76.2% (48)	2.4 : 7.6 23.8%(15) 76.2%(48)	2.6 : 7.4 25.8%(16) 74.2%(46)	2.1 : 7.9 21.0%(13) 79.0%(49)	**ns** p=0.938
Referral source GDP GP Specialist	 92.1% (58) 3.2% (2) 4.8% (3)	 88.9% (56) 4.8% (3) 6.3% (4)	 93% (56) 1.6% (1) 8.1% (5)	 96.8% (60) 0% (0) 3.2% (2)	**ns** p=0.551
Employment status Employed Unemployed Student Retired (medical) House wife	 66.7% (42) 7.9% (5) 14.3% (9) 1.6% (1) 9.5% (6)	 69.8%(44) 6.3% (4) 11.1%(7) 0% (0) 12.7%(8)	 64.5%(40) 6.5% (4) 22.6%(14) 0% (0) 6.5% (4)	 66.1%(41) 9.7% (6) 14.5%(9) 0% (0) 9.7% (6)	**ns** p=0.797
Socio-economic status Professional I Intermmediate IIi Skilled non-manual IIii Skilled manual III Semi skilled IV Unskilled V Unemployed, house wife, student, medically retired VI	 7.9% (5) 27.0% (17) 23.8% (15) 6.3% (4) 1.6% (1) 0% (0) 31.7% (20)	 4.8% (3) 30.2%(19) 31.7%(20) 1.6% (1) 1.6% (1) 0% (0) 30.2%(19)	 1.6% (1) 43.5%(27) 16.1%(10) 1.6% (1) 1.6% (1) 0% (0) 35.5%(22)	 3.2% (2) 24.2%(15) 33.9%(21) 3.2% (2) 3.2% (2) 1.6% (1) 30.6%(19)	**ns** p=0.398
Marital status Single Married Seperated Divorced Widowed	 61.9% (39) 30.2% (19) 1.6% (1) 6.3% (4) 0% (0)	 55.6%(35) 41.3%(26) 0% (0) 3.2% (2) 0% (0)	 62.9%(39) 33.8%(21) 0% (0) 3.2% (2) 0% (0)	 54.8%(34) 37.1%(23) 1.6% (1) 4.8% (3) 1.6% (1)	**ns** p=0.511

Group 1 (SSRI), Group 2 (Placebo), Group 3 (Splint), Group 4 (SSRI and splint)

Significance test, Chi-squared (One way ANOVA for age and duration) all **ns**.

6.2.2 CLINICAL HISTORY

6.2.2 Clinical history

6.2.2.1 TMJ symptoms (Figure 23, Table 11)

TMJ pain was a universal symptom amongst the patient cohort, due to the studies specified inclusion criteria. Additionally, commonly reported symptoms included muscle pain 100/250 (40%), clicking 192/250 (76.8%) and limitation in mouth opening 187/250 (74.8%).

6.2.2.2 Character and location of TMJ pain (Figure 24, Table11)

Patients generally described their pain as a dull ache 161/250 (64%) and or discomfort 137/250 (54.8%). A description of sharp pain was also reported by 99/250 (39.6%). Location of pain was predominantly unilateral 180/250 (72%) compared to bilateral 70/250 (28%).

6.2.2.3. Frequency (Table 12)

TMJ pain was recorded as always, often or occasionally present. The majority reported pain to be always present 151/250 (60.4%), often 83/250 (33.2%) and occasionally 16/250 (6.4%). In some cases, patients in the always and often categories gave further clarification to their response. Always dull but occasionally sharp 54/250 (21.6%) or often dull but occasionally sharp 6/250 (2.4%).

6.2.2.4 Length and frequency of bouts (Table 12)

Bouts of pain length were recorded as constant, weeks, days , hours or minutes in duration. The majority of patients reported constant pain 185/250 (74.0%). Frequency of occurrence was described as constant 185/250 (74%), daily 43/250 (17.2%), weekly 19/250 (7.6%) or monthly 3/250 (1.2%).

6.2.2.5 Pain free intervals (Table 12)

Time intervals of pain remission ranged from none for constant pain 185/250 (74%) to days 51/250 (20.4%) or weeks 14/250 (5.6%) in duration.

6.2.2.6 Diurnal variation (Table13)

The intensity of pain throughout the day was ascertained. The majority reported pain worst in the mornings 113/250 (45.2%). 70/250 (28%) described pain to be worse in the evening and 67/250 (26.8%) the same intensity throughout the day.

6.2.2.7 Altered sleep patterns (Table 13)

Patients reported a range of sleep disorders related to pain, including prevention of sleep 113/250 (45.2%) and disturbance of sleep 117/250 (46.8%).

Sleep problems specifically related to current TMJ pain were variable. 98/250 (39.2%) reported no problems, 34/250 (13.6%) were unable to get to sleep, 58/250 (23.2%) experienced disturbed sleep whilst 8/250 (3.2%) suffered from early morning waking. A combination of sleep disorders occurred in some individuals with difficulty getting to sleep and disturbed sleep in 22/250 (8.8%), difficulty getting to sleep and early waking in 3/250 (1.2%), disturbed sleep and early waking in 13/250 (5.2%) and difficulty getting to sleep, disturbed sleep and early waking in 14/250 (5.6%)

6.2.2.8 Nocturnal bruxism and disturbed occlusal discomfort

Only 49/250 (19.6%) believed they had a nocturnal bruxism habit but 133/250 (53.2%) reported a sensation of disturbed occlusal comfort.

6.2.2.9 Precipitating factors for TMJ pain (Figure 25, Table 14)

The precipitants were recalled by study participants to be; none 67/250 (26.8%),dental in origin 66/250 (26.4%), following an infection 60/250 (24.0%) due to physical trauma 39/250 (15.6%) or emotional trauma 7/250 (2.8%).

6.2.2.10 Provocation of TMJ pain (Figure 26, Table 14)

These were principally related to jaw movement; chewing 192/250 (76.8%), yawning 191/250 (76.4%) and biting 164/250 (65.6%). An association with emotional distress was however indicated in 134/250 (53.6%) and cold weather 72/250 (28.8%).

6.2.2.11 Relief of TMJ pain (Figure 27, Table 15)

The use of analgesics, in an attempt to alleviate pain was described by 132/250 (52.8%). Other commonly reported techniques were resting the jaw 110/250 (44%), the application of pressure 96/250 (38.4%) or application of warmth 60/250,(24%).

6.2.2.12 Other chronic pain conditions (Figure 28, Table 16)

The majority of participants gave an account of other recurrent chronic pain conditions. These were most notably headaches 153/250 (61.2%), neckache 125/250 (50%) and backache 121/250 (48.4%). Nearly a third of patients also reported migraine 82/250 (32.8%) and abdominal pain 75/250 (29.6%).

All reported symptoms were not statistically significant between groups.

Figure 23: TMJ symptoms

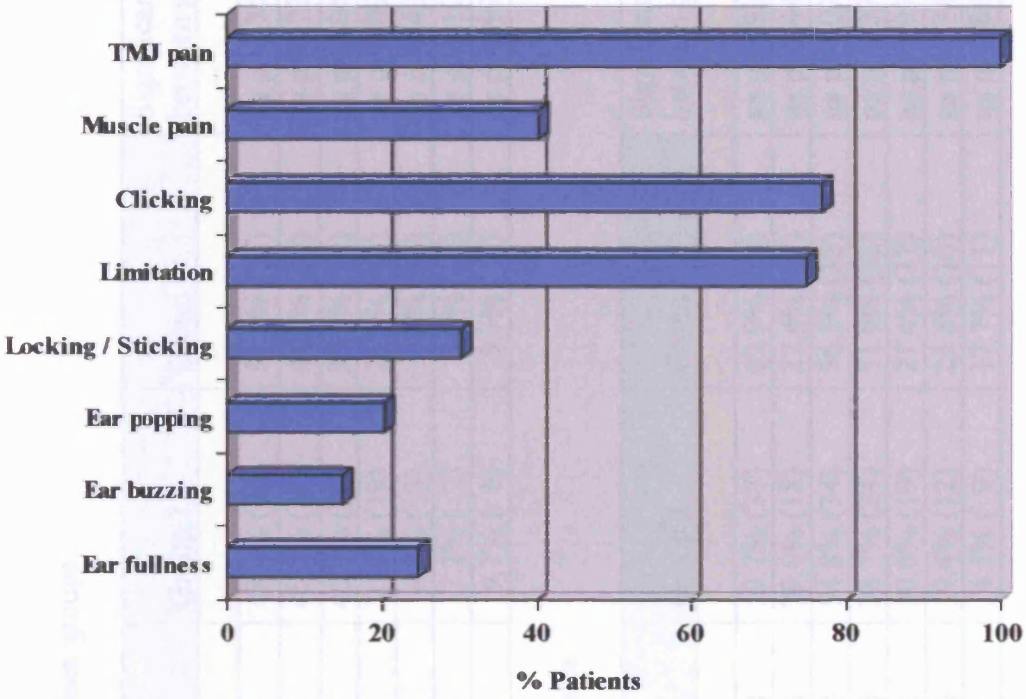


Figure 24: TMJ pain character

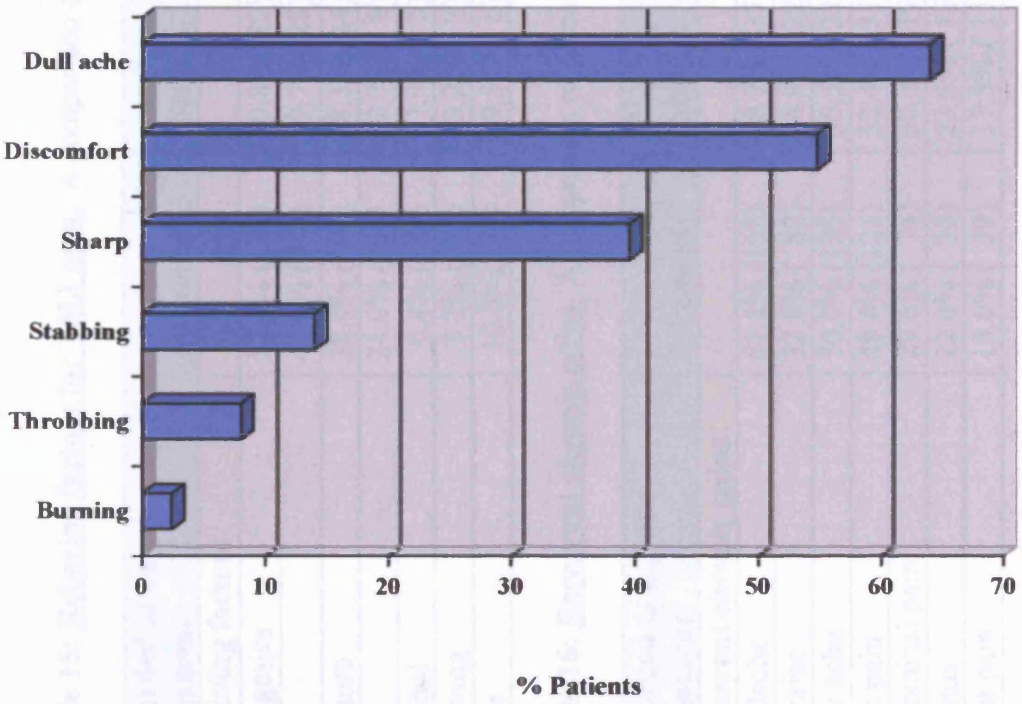


Table 15: Relieving factors for TMJ pain. A comparison of percentages between groups.

Recorded at baseline assessment	All groups	Group 1	Group 2	Group 3	Group 4	Significance between gps.
Relieving factors						
Analgesics	52.8% (132)	50.8% (32)	57.1% (36)	48.4% (30)	54.8% (34)	**ns** p=0.761
Rest	44.0% (110)	39.7% (25)	49.2% (31)	45.2% (28)	41.9% (26)	**ns** p=0.727
Pressure	38.4% (96)	38.1% (24)	39.7% (25)	40.3% (25)	35.5% (22)	**ns** p=0.947
Heat	24.0% (60)	12.7% (8)	27.0% (17)	30.6% (19)	25.8% (16)	**ns** p=0.097
Alcohol	6.4% (16)	7.9% (5)	3.2% (2)	4.8% (3)	9.7% (6)	**ns** p=0.439
Chewing	3.2% (8)	3.2% (2)	3.2% (2)	3.2% (2)	3.2% (2)	**ns** p=0.100
Other	10.0%(25)	9.5% (6)	11.1%(7)	9.7% (6)	9.7% (6)	**ns** p=0.990

Table 16: Recurrent chronic pains A comparison of percentages between groups

Recorded at baseline assessment	All groups	Group 1	Group 2	Group 3	Group 4	Significance between gps.
Recurrent chronic pains						
Headache	61.2% (153)	58.7% (37)	63.5% (40)	59.7% (37)	62.9% (39)	**ns** p=0.932
Migraine	32.8% (82)	34.9% (22)	39.7% (25)	29.0% (18)	27.4% (17)	**ns** p=0.441
Neck ache	50.0% (125)	36.5% (23)	52.4% (33)	54.8% (34)	56.5% (35)	**ns** p=0.096
Back pain	48.4% (121)	52.4% (33)	50.8% (32)	38.7% (24)	51.6% (32)	**ns** p=0.372
Abdominal pain	29.6% (74)	30.2% (19)	30.2% (19)	30.6% (19)	27.4% (17)	**ns** p=0.979
Pruritus	22.0% (55)	23.8% (15)	19.0% (12)	19.4% (12)	25.8% (16)	**ns** p=0.749
Chest pain	15.6% (39)	17.5% (11)	12.7% (8)	14.5% (9)	17.7% (11)	**ns** p=0.840

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Chi squared non significant between groups

Table 14: Precipitating and provoking factors for TMJ pain. A comparison of percentages between groups.

Base line record	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
Precipitating factors						
Dental	26.4% (66)	23.8% (15)	30.2% (19)	21% (13)	21% (13)	**ns** p=0.533
Physical trauma	15.6% (39)	25.4% (16)	12.7% (8)	11.3%(7)	11.3%(7)	**ns** p=0.102
Emotional trauma	2.8% (7)	4.8% (3)	3.2% (2)	1.6% (1)	1.6% (1)	**ns** p=0.186
Infection	24.0% (60)	15.9% (10)	22.2% (14)	32.3%(20)	32.3%(20)	**ns** p=0.667
None	26.8% (67)	33.3% (21)	31.7% (20)	27.4%(17)	27.4%(17)	**ns** p=0.074
Provoking factors						
Chewing	76.8% (192)	77.8% (49)	73.0% (46)	80.6% (50)	75.8% (47)	**ns** p=0.780
Yawning	76.4% (191)	71.4% (45)	79.4% (50)	75.8% (47)	79.0% (49)	**ns** p=0.701
Biting	65.6% (164)	58.7% (37)	69.8% (44)	66.1% (41)	67.7% (42)	**ns** p=0.582
Emotional tension	53.6% (134)	50.8% (32)	50.8% (32)	58.1% (36)	54.8% (34)	**ns** p=0.817
Talking	31.6% (79)	33.3% (21)	34.9% (22)	24.2% (15)	33.9% (21)	**ns** p=0.546
Cold weather	28.8% (72)	23.8% (15)	38.1% (24)	29.0% (18)	24.2% (12)	**ns** p=0.255
Hot weather	2.4% (6)	3.2% (2)	1.6% (1)	4.8% (3)	0% (0)	**ns** p=0.329
Hot food/drink	1.6% (4)	0% (0)	1.6% (1)	1.6% (1)	3.2% (2)	**ns** p=0.559
Cold food/drink	2.4% (6)	1.6%(1)	1.6% (1)	3.2% (2)	3.2% (2)	**ns** p=0.869
Alcohol	3.2% (8)	6.3%(4)	1.6% (1)	1.6% (1)	3.2% (2)	**ns** p=0.384
Chocolate	2.0% (5)	0%(0)	0% (0)	1.6% (1)	6.5% (4)	**ns** p=0.031
Cheese	1.6% (4)	0%(0)	1.6% (1)	1.6% (1)	3.2% (2)	**ns** p=0.559
Other	4.4% (11)	3.2%(2)	1.6% (1)	4.8% (3)	8.1% (5)	**ns** p=0.332

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Chi squared non significant between groups

Table 13: Diurnal variation, sleep and bruxism habits. A comparison of intergroup percentages.(N=250)

	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
Diurnal variation in TMJ pain						
Worse in the morning	113 (45.2%)	26 (41.3%)	25 (39.7%)	32 (51.6%)	30 (48.4%)	**ns** p=0.484
Worse in the evening	70 (28.0%)	17 (27%)	20 (31.7%)	16 (25.8%)	17 (27.4%)	**ns** p=0.890
No variation						
Altered sleep patterns						
Prevention of sleep	113 (45.2%)	29 (46%)	28 (44.4%)	27 (43.5%)	29 (46.8%)	**ns** p=0.983
Disturbance of sleep	117 (46.8%)	29 (46%)	28 (44.4%)	31 (50%)	29 (46.8%)	**ns** p=0.938
No problems	98 (39.4%)	25 (39.7%)	22 (34.9%)	27 (43.5%)	24 (38.7%)	
Cannot get to sleep	33 (13.2%)	10 (15.9%)	9 (14.3%)	4 (6.5%)	11 (17.7%)	
Disturbed sleep	58 (23.2%)	13 (20.6%)	16(25.4%)	16 (25.8%)	13 (21.0%)	
Early morning waking	8 (3.2%)	2 (3.2%)	3 (4.8%)	1 (1.6%)	2 (3.2%)	
Cannot get to sleep and disturbed sleep	22 (8.8%)	5 (7.9%)	5 (7.9%)	7 (11.3%)	5 (8.1%)	**ns** p=0.919
Cannot get to sleep and early waking	3 (1.2%)	2 (3.2%)	1 (1.6%)	0 (0%)	0 (0%)	
Disturbed sleep and early waking	13 (5.2%)	3 (4.8%)	3 (4.8%)	5 (8.1%)	2 (3.2%)	
Cannot get to sleep, disturbed sleep and early morning waking	14 (5.6%)	3 (4.8%)	4 (6.3%)	2 (3.2%)	5 (8.1%)	
Bruxism and occlusal comfort						
Nocturnal bruxism habit	49 (19.6%)	15 (23.8%)	11 (17.5%)	8 (12.9%)	15 (24.2%)	**ns** p=0.323
Sensation of disturbed occlusal comfort	133 (53.2%)	31 (49.2%)	25 (39.7%)	40 (64.5%)	37 (59.7%)	**ns** p=0.026

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Chi squared non significant between groups

Figure 25: TMJ pain - Precipitating factors

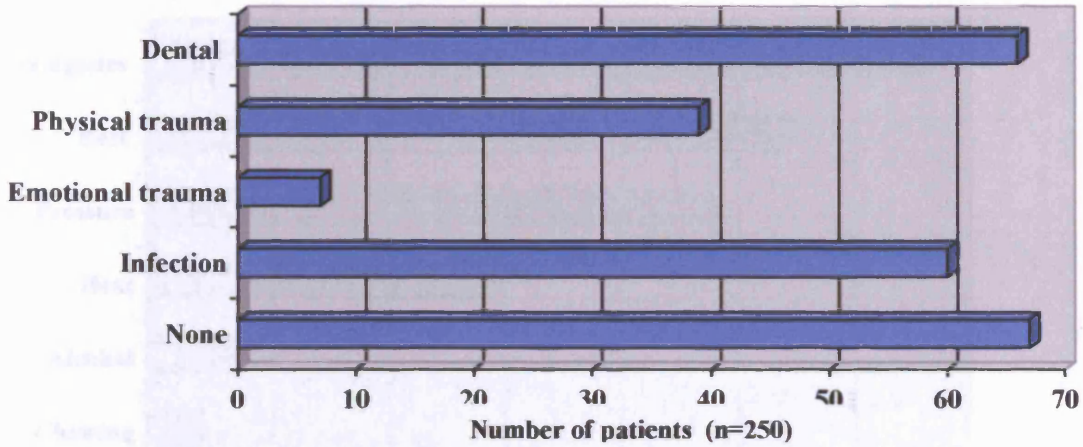


Figure 26: TMJ pain - Provoking factors

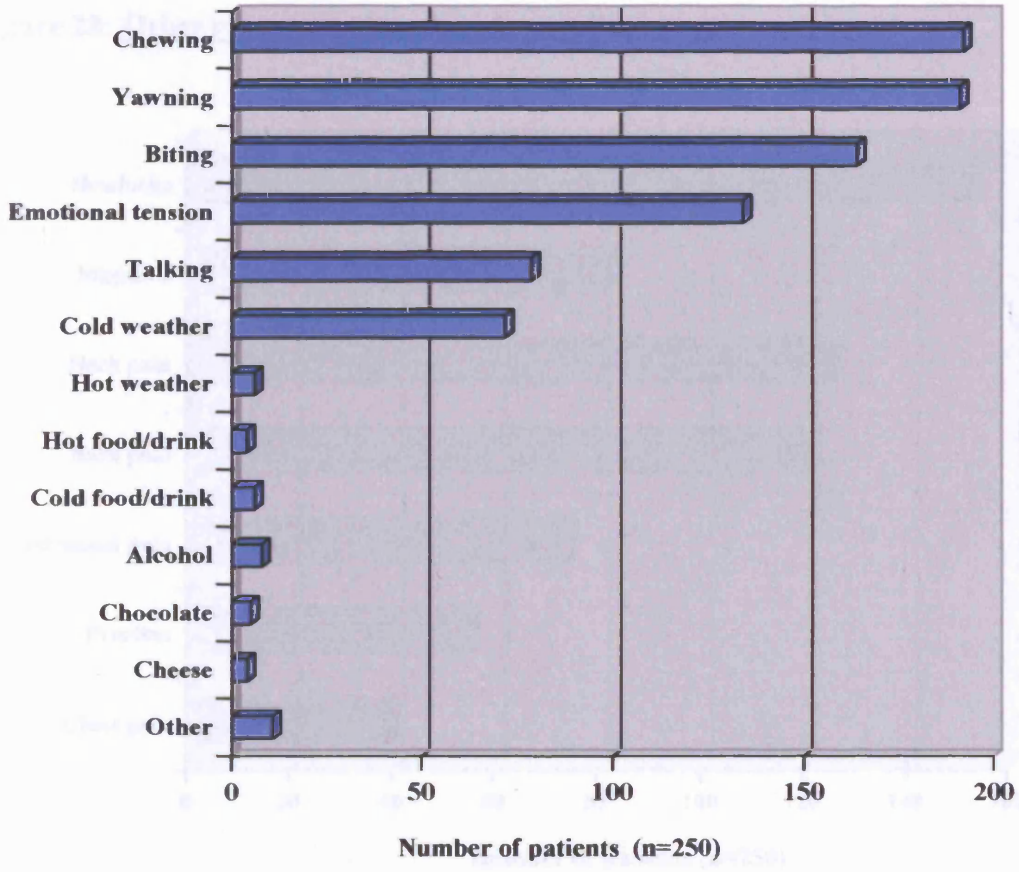


Figure 27: TMJ pain - Relieving factors

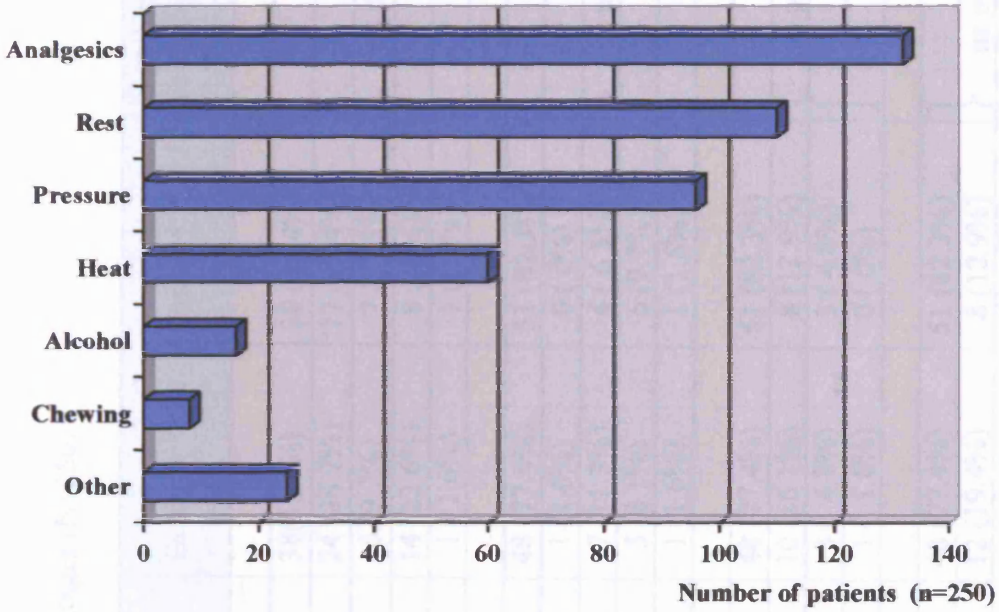


Figure 28: Other recurrent chronic pain conditions

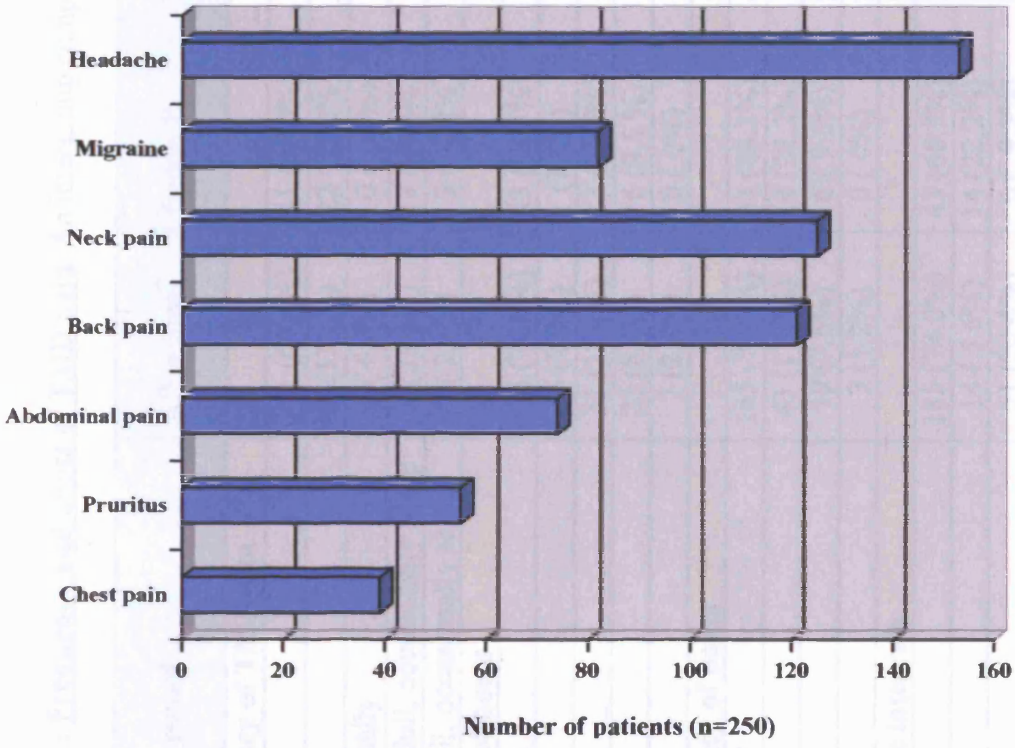


Table 12: Frequency and bouts of TMD pain An intergroup comparison of percentages.(N=250)

Baseline record	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
Frequency of TMJ pain						
Always	151 (60.4%)	41 (65.0%)	40 (63.4%)	38(51.6%)	38 (61.4%)	
Often	83 (33.2%)	22 (35.0%)	20 (31.8%)	24 (38.7%)	17 (27.4%)	
Occasionally	16 (6.4%)	0 (0%)	3 (4.8%)	6 (9.7%)	7 (11.3%)	**ns** p=0.185
Always dull, occasionally sharp	54 (21.6%)	13 (20.6%)	19 (30.1%)	14 (22.6%)	8 (13%)	
Often dull, occasionally sharp	6 (2.4%)	3 (4.8%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	
Length of bouts						
Constant	185 (74.0%)	43 (68.3%)	43 (68.3%)	48 (77.4%)	51 (82.3%)	
Weeks	5 (2.0%)	1 (1.6%)	3 (4.8%)	1 (1.6%)	0 (0%)	
Days	31 (12.4%)	13 (20.6%)	7 (11.1%)	7 (11.3%)	4 (6.5%)	**ns** p=0.092
Hours	22 (8.8%)	6 (9.5 %)	5 (7.9%)	5 (8.1%)	6 (9.7%)	
Minutes	7 (2.8%)	0 (0%)	5 (7.9%)	1 (1.6%)	1 (1.6%)	
Frequency of bouts						
Constant	185 (74.0%)	43 (68.3%)	43 (68.3%)	48 (77.4%)	51 (82.3%)	
Daily	43 (17.2%)	14 (22.2%)	11 (17.5%)	10 (16.1%)	8 (12.9%)	**ns** p=0.431
Weekly	19 (7.6%)	6 (9.5%)	7 (11.1%)	3 (4.8%)	3 (4.8%)	
Monthly	3 (1.2%)	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	
Pain free intervals						
None	185 (74.0%)	43 (68.3%)	43 (68.3%)	48 (77.4%)	51 (82.3%)	
Weeks	14 (5.6%)	14 (22.2%)	17 (27.0%)	12 (19.4%)	8 (12.9%)	**ns** p=0.329
Days	51 (20.4%)	6 (9.5%)	3 (4.8%)	2 (3.2%)	3 (4.8%)	

Group 1 – Fluoxetine medication Group 3 – Splint therapy Chi squared non significant between groups
Group 2 – Placebo medication Group 4 – Fluoxetine and splint therapy

Table 11: TMD symptoms A comparison of percentages between groups.(N=250)

Baseline record prior to treatment	**All groups** (n=250)	**Group 1** (n=63)	**Group 2** (n=63)	**Group 3** (n=62)	**Group 4** (n=62)	Significance between groups
TMJ symptoms						
TMJ pain	250 (100%)	63 (100%)	63 (100%)	62 (100%)	62 (100%)	**ns** p=1.0
Muscle pain – Temporalis	65 (26%)	12 (19%)	17 (27%)	23 (37.1%)	13 (21%)	**ns** p=0.094
Muscle pain - Masseter	80 (32%)	14 (22.2%)	25 (39.7%)	20 (32.3%)	21 (33.9%)	**ns** p=0.205
Clicking	192 (76.8%)	50 (79.4%)	45 (71.4%)	52 (83.9%)	45 (72.6%)	**ns** p=0.307
Sticking	76 (30.4%)	21 (33.3%)	12 (19.0%)	24 (38.7%)	19 (30.6%)	**ns** p=0.106
Locking	19 (7.6%)	4 (6.3%)	5 (7.9%)	6 (9.7%)	4 (6.5%)	**ns** p=0.815
Limitation in mouth opening	187 (74.8%)	51 (81%)	40 (63.5%)	48 (77.4%)	48 (77.4%)	**ns** p=0.112
Ear popping	51 (20.4%)	10 (15.9%)	14 (22.2%)	10 (16.2%)	17 (27.4%)	**ns** p=0.451
Ear buzzing	37 (14.8%)	6 (9.5%)	12 (19%)	11 (17.8%)	8 (12.9%)	**ns** p=0.673
Ear deafness	37 (14.8%)	7 (11.1%)	9 (14.3%)	7 (11.3%)	14 (22.6%)	**ns** p=0.563
Ear fullness	62 (24.8%)	16 (25.4%)	20 (31.7%)	12 (19.4%)	14 (22.6%)	**ns** p=0.408
Character and location of TMJ pain						
Dull ache	161 (64.4%)	43 (68.3%)	33 (52.4%)	45 (72.6%)	40 (64.5%)	**ns** p=0.103
Discomfort	137 (54.8%)	35 (55.6%)	37 (58.7%)	33 (53.2%)	32 (51.6%)	**ns** p=0.868
Sharp	99 (39.6%)	27 (42.9%)	30 (47.6%)	17 (27.4%)	25 (40.3%)	**ns** p=0.120
Stabbing	35 (14%)	9 (14.3%)	7 (11.1%)	14 (22.6%)	5 (8.1%)	**ns** p=0.109
Throbbing	20 (8%)	3 (4.8%)	6 (9.5%)	4 (6.5%)	7 (11.3%)	**ns** p=0.530
Burning	6 (2.4%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.8%)	**ns** p=0.553
Unilateral	180 (72%)	45 (71.4%)	47 (74.6%)	43 (69.4%)	45 (72.6%)	**ns** p=0.930

Group 1 – Fluoxetine medication Group 3 – Splint therapy Chi squared nonsignificant between groups
Group 2 – Placebo medication Group 4 – Fluoxetine and splint therapy

6.2.3 CLINICAL EXAMINATION

6.2.3 Clinical examination

6.2.3.1 Extra oral examination

6.2.3.1.1 TMJ signs (Figure 29, Table 17)

On examination all patients had TMJ pain 250/250 (100%), predominantly unilateral in nature 168/250 (66%).In addition patients had associated muscle tenderness to palpation (57%),TMJ clicking (35%) and limitation in mouth opening exhibited in 45/250 (18%).

6.2.3.1.2 Interincisal mouth opening (Figure 30, Table 17)

Interincisal mouth opening was measured from the incisal margin of the maxillary central incisor to the opposing incisal margin of the mandibular incisor. The mean measurement was 38.9mm (SD 9.35) (range 15-60mm). Limitation in mouth opening was taken to be less than 30mm.

6.2.3.2 Intra oral examination

6.2.3.2.1 Buccal and lingual soft tissues (Table 18)

On intra oral examination of the soft tissues evidence of bruxism or clenching was noted. Ridging of the buccal mucosa was present in over half the patients 132/250 (52.8%) and scalloped margin of the lateral border of the tongue in 31/219 (12.4%).

6.2.3.2.2 Occlusion and dentition (Table 18)

Occlusally the majority of patients were class I malocclusion 98/250 (39.2%) or class II division I malocclusion 95/250 (38%). 158/250 (63.2%) of patients had one wisdom tooth removed or missing and 79/250 (31.6%) had four removed or missing posterior molar teeth.

6.2.3.3 Intergroup ananlysis (Table 17 and 18)

No siginificant difference was observed between groups in intra and extra oral examinations.

Clinical examination

Extra oral examination

Figure 29: TMJ signs

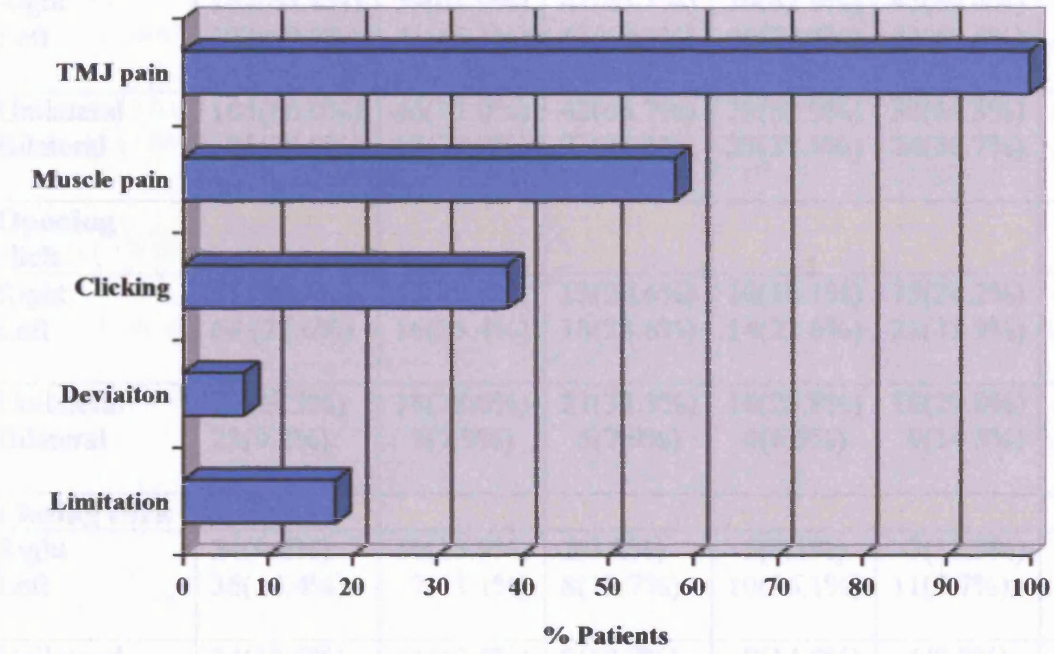
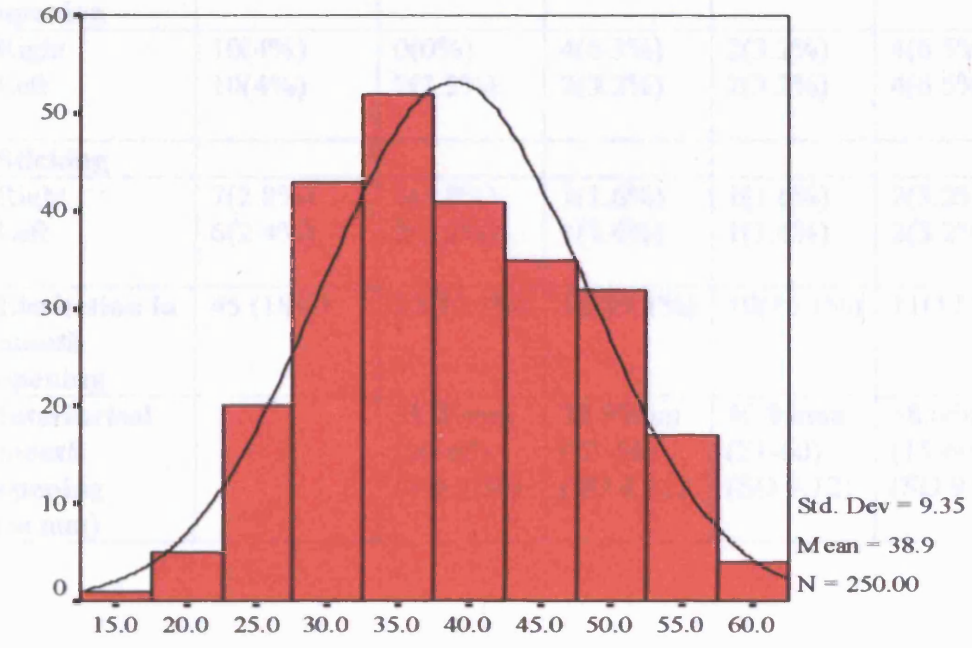


Figure 30: Interincisal mouth opening



TMJ interincisal opening, baseline

Table 17: Extra oral examination -TMJ signs,– intergroup analysis (N=250)

Baseline recordings	All groups	Group 1	Group 2	Group 3	Group 4	Sig.
TMJ pain						
Right	162(64.8%)	39(61.9%)	41(65.1%)	39(62.9%)	43(69.4%)	ns
Left	173(69.2%)	41(65.1%)	43(68.3%)	46(74.2%)	43(69.4%)	ns
Unilateral	165(66.0%)	46(73.0%)	42(66.7%)	39(62.9%)	38(61.3%)	ns
Bilateral	85(34.0%)	17(27.0%)	21(33.3%)	23(37.1%)	24(38.7%)	ns
Opening click						
Right	51 (20.4%)	13(20.6%)	13(20.6%)	10(16.1%)	15(24.2%)	ns
Left	69 (27.6%)	16(25.4%)	18(28.6%)	14(22.6%)	21(33.9%)	ns
Unilateral	73(29.2%)	18(28.6%)	21(33.3%)	16(25.8%)	18(29.0%)	ns
Bilateral	23(9.2%)	5(7.9%)	5(7.9%)	4(6.5%)	9(14.5%)	ns
Closing click						
Right	24(9.6%)	10(15.9%)	2(3.2%)	5(8.1%)	7(11.3%)	ns
Left	36(14.4%)	7(11.1%)	8(12.7%)	10(16.1%)	11(7.7%)	
Unilateral	34(13.6%)	11(17.5%)	8(12.7%)	9(14.5%)	6(9.7%)	ns
Bilateral	13(5.2%)	3(4.8%)	1(1.6%)	3(4.8%)	6(9.7%)	
Deviation on mouth opening						
Right	10(4%)	0(0%)	4(6.3%)	2(3.2%)	4(6.5%)	ns
Left	10(4%)	2(3.2%)	2(3.2%)	2(3.2%)	4(6.5%)	ns
Sticking						
Right	7(2.8%)	3(4.8%)	1(1.6%)	1(1.6%)	2(3.2%)	ns
Left	6(2.4%)	2(3.2%)	1(1.6%)	1(1.6%)	2(3.2%)	ns
Limitation in mouth opening	45 (18%)	12(19.1%)	12(19.1%)	10(16.1%)	11(17.7%)	ns
Interincisal mouth opening (in mm)		38.29mm (20-60) (SD 9.58)	38.90mm (23-56) (SD 8.31)	40.85mm (21-60) (SD 9.12)	38.66mm (15-60) (SD 9.87)	ns

Table 18: Intra oral examination – inter group analysis (N=250)

Recorded at baseline assessment	n=63 **Group 1** (Fluoxetine) (SSRI)	n=63 **Group 2** (Placebo)	n=62 **Group 3** (Splint)	n=62 **Group 4** (Splint and Fluoxetine)	Sig
Occlusion Angles classification					
Class I	20 (31.7%)	22(34.9%)	27(43.5%)	29(46.8%)	**ns**
Class II division i	27 (42.9%)	27(42.9%)	21(33.9%)	20(32.3%)	
Class II division ii	14 (22.2%)	13(20.6%)	14(22.6%)	13(21.0%)	
Class III	2 (3.2%)	1(1.6%)	0(0%)	0(0%)	
Overjet > 6mm	1 (1.6%)	4(6.4%)	1(1.6%)	3(4.8%)	**ns**
Buccal mucosa					
Ridging	32 (50.8%)	30(47.6%)	41(66.1%)	29(46.8%)	**ns**
Frictional keratosis	3 (4.8%)	3(4.8%)	5(8.1%)	4(6.5%)	
Abrasion	2 (3.2%)	3(4.8%)	1(1.6%)	1(1.6%)	
Ulcer	0 (0%)	1(1.6%)	0(0%)	0(0%)	
Lingual mucosa Ridging (scalopped margin)	8 (12.7%)	6 (9.5%)	8 (12.9%)	9 (14.5%)	**ns**
Missing posterior teeth					
None	19 (30.2%)	19(30.2%)	21(33.9%)	21(33.9%)	**ns**
One	2 (3.2%)	4(6.3%)	4(6.5%)	3(4.8%)	
Two	9 (14.3%)	9(14.3%)	9(14.5%)	8(12.9%)	
Three	6 (9.5%)	3(4.8%)	6(9.7%)	3(4.8%)	
Four	21 (33.3%)	17(27.0%)	18(29%)	23(37.1%)	
More than five	6 (9.5%)	11(17.5%)	4(6.5%)	4(6.5%)	
Missing wisdom teeth					
None	20 (36.8%)	22(34.9%)	24(38.7%)	26(41.9%)	**ns**
One	4 (6.3%)	3(4.8%)	4(6.5%)	4(6.5%)	
Two	11 (17.5%)	11(17.5%)	11(17.7%)	6(9.7%)	
Three	5 (7.9%)	5(7.9%)	7(11.3%)	5(8.1%)	
Four	23 (36.5%)	22(34.9%)	16(25.8%)	21(33.9%)	
Missing maxillary canine tooth	2 (3.2%)	1 (1.6%)	2 (3.2%)	2 (3.2%)	**ns**

Significance test, Chi-squared (One way ANOVA for age and duration) all **ns**.

6.2.4 SELF- REPORT PAIN ASSESSMENT QUESTIONNAIRES

BASELINE SCORES

6.2.4.0 Self-report questionnaires (Table 18a,b)

The MPI, MPQ, BDI and Kellner questionnaires were completed by the patients prior to clinical consultations.

6.2.4.1 Multidimensional pain inventory (MPI) (Table 18a)

The MPI scores ranged from 0-6 and average scores were recorded as median (25^{th} and 75^{th} percentiles). Analysing the patient's perspective of pain and impact on daily life mid-range scores were observed by the majority of individuals in MPI : severity mean 3.00 (1.83,4.00) life control 3.25 (1.50,3.87) and affective distress 3.33 (2.33,4.00).

Again mid-range scores were observed for the supportive response 3.33 (2.30,4.66) and solicitous response 2.66 (1.50,3.87) of a significant person in the patient's life.

Frequency of patient participation in common daily activities was slightly above mid-range, household chores 4.80 (3.60,5.60), activities away from home 3.50 (2.75,4.25), social activites 3.00 (2.30,4.00) and general activity level 3.38 (2.75,3.91).

6.2.4.2 McGill Pain Questionnaire (MPQ) (Table 18b)

The scores on average were not consistent with severe pain. The median VAS (range 0-10) was 2.90 (1.20,5.45), PPI (range 0-5) 2.00 (1.00,2.00), MPQ total % (range 0-100) 31.00 (20.00,47.00), MPQ sensory % (range 0-100) 33.00 (21.00,45.00) and MPQ affective % (range 0-100) 17.00 (3.00,42.00).

6.2.4.3 Beck Depression Index (BDI) (Table 18b)

The median composite depression score for this cohort of patients was 7.00 (3.00,13.00) which would indicate the majority of patients were not suffering from depression, despite experiencing chronic pain.

6.2.4.4 Kellner (Table 18b)

Illness attitude (range 0-30), hypocondriacal beliefs (range 0-15) and disease phobia (range 0-15) were relatively low and within a normal range with median scores of 8.00 (6.00,11.00), 3.00 (3.00,6.00) and 3.00 (3.00,5.00) respectively.

6.2.4.5 Intergroup analsis (Table 18a,b)

Results revealed no significant difference between groups suggesting a homogeneity in randomisation.

Table 18a : Multidimensional pain inventory (MPI) A comparison of median scores (25th and 75th percentiles) (range 0-6)

MPI Baseline recordings	(n=250) All groups	(n=63) Group 1	(n=63) Group 2	(n=62) Group 3	(n=62) Group 4	Significance between groups
Patients perspective of pain and impact on daily life						
MPI – Severity	3.00 (1.83,4.00)	3.33 (2.00,4.33)	3.00 (2.33,4.00)	2.66 (1.33,3.40)	2.66 (1.65,4.00)	**ns** p=0.105
MPI - Interference	1.36 (0.55,2.82)	1.45 (0.55,3.00)	1.63 (0.80,2.90)	1.36 (0.45,2.27)	1.19 (0.45,2.65)	**ns** p=0.427
MPI – Life control	3.25 (2.31,4.00)	3.25 (2.00,4.00)	3.25 (2.25,4.25)	3.25 (2.46,4.00)	3.38 (2.50,4.25)	**ns** p=0.780
MPI – Affective distress	3.33 (2.33,4.30)	3.33 (2.33,4.30)	3.60 (2.65,4.40)	3.00 (2.00,4.00)	3.32 (2.32,4.30)	**ns** p=0.058
Response of significant other person to patient						
MPI – Support response	3.33 (2.30,4.66)	3.60 (2.25,4.66)	3.66 (2.32,5.00)	3.00 (2.33,4.33)	3.00 (2.00,4.33)	**ns** p=0.681
MPI – Punishing response	1.00 (0,2.06)	0.75 (0.25,2.81)	1.25 (0.25,2.56)	0.75 (0,2.00)	0.75 (0,1.75)	**ns** p=0.201
MPI – Solicitous response	2.66 (1.50,3.87)	2.83 (1.45,3.63)	2.66 (1.77,4.37)	2.66 (1.50,3.83)	2.50 (1.30,3.83)	**ns** p=0.929
MPI – Distracting response	1.75 (0.75,2.75)	2.00 (0.75,2.75)	1.50 (0.75,3.00)	2.00 (0.75,2.75)	1.75 (0.50,3.00)	**ns** p=0.959
Frequency of participation in common activities						
MPI – Household chores	4.80 (3.60,5.60)	4.80 (3.60,5.60)	4.80 (3.35,5.80)	4.60 (3.40,5.80)	4.80 (3.80,5.40)	**ns** p=0.961
MPI – Outdoor work	2.00 (1.00,3.00)	1.90 (1.28,3.00)	1.90 (0.81,3.15)	2.00 (0.95,3.00)	2.00 (0.80,3.00)	**ns** p=0.749
MPI – Activities away from home	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.75 (2.75,4.50)	3.25 (2.25,4.25)	3.50 (2.50,4.50)	**ns** p=0.714
MPI – Social activities	3.00 (2.30,4.00)	2.75 (2.25,3.75)	3.25 (2.50,4.00)	3.00 (2.33,3.75)	3.38 (2.00,4.01)	**ns** p=0.655
MPI – General activity level	3.38 (2.75,3.91)	3.40 (2.80,3.88)	3.44 (2.68,3.84)	3.31 (2.50,3.79)	3.34 (2.80,4.05)	**ns** p=0.901

Table 18b : McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale.(Kellner)
A comparison of median scores (25th and 75th percentiles)Baseline recordings, prior to treatment.

Self report Questionnaire	(n=250) All groups	(n=63) Group 1	(n=63) Group 2	(n=62) Group 3	(n=62) Group 4	Significance between groups
MPQ						
Visual analogue scale (VAS) (range 0-10)	2.90 (1.20,5.45)	2.90 (1.20,6.03)	3.30 (1.60,5.60)	2.70 (1.23,4.80)	2.75 (0.90,5.38)	ns p=0.881
Present pain intensity (PPI) (range 0-5)	2.00 (1.00,2.00)	2.00 (1.00,3.00)	2.00 (1.00,2.00)	2.00 (1.00,2.00)	2.00 (1.00,2.00)	ns p=0.617
MPQ – total % (range 0-100)	31.00 (20.0,47.00)	35.50 (23.50,47.00)	31.00 (19.5,40.0)	30.00 (18.00,39.50)	31.00 (18.00,50.00)	ns p=0.384
MPQ– sensory % (range 0-100)	33.00 (21.0,45.00)	39.00 (26.25,48.00)	31.00 (21.00,45.00)	33.00 (21.00,42.00)	33.00 (19.50,50.00)	ns p=0.339
MPQ – affective % (range 0-100)	17.00 (3.00,42.00)	25.00 (0, 52.00)	17.00 (8.00,40.50)	17.00 (8.00,25.00)	17.00 (0,50.00)	ns p=0.663
BDI						
Composite score (range 0-45)	7.00 (3.00,13.00)	7.00 (2.25,13.75)	7.00 (3.00,11.00)	6.00 (2.00,10.50)	8.00 (4.25,14.75)	ns p=0.344
Kellner						
Illness attitude- total (range 0-30)	8.00 (6.00,11.00)	8.00 (6.00,11.50)	7.00 (6.00,9.50)	7.50 (6.00,11.00)	8.00 (6.00,12.00)	ns p=0.206
Hypochondriacal beliefs (range 0-15)	3.00 (3.00,6.00)	4.00 (3.00,6.00)	3.00 (3.0,5.00)	3.00 (3.00,6.00)	3.00 (3.00,6.00)	ns p=0.477
Disease phobia (range 0-15)	3.00 (3.00,5.00)	3.00 (3.00,5.50)	3.00 (3.00,4.00)	3.00 (3.00,6.00)	4.00 (3.00,7.00)	ns p=0.112

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

VI DISCUSSION

6.4 Demographics and epidemiological features of the study cohort

Hypothesis (2)

The demographic and epidemiological features of the study cohort, are consistent with the patient population seen within a secondary and tertiary TMJ clinic.

It is acknowledged that a clinic environment does not represent the prevalence of TMD amongst the overall population,(Drangsholt and Le Resche,1999). However, this hypothesis was to investigate this specific TMD clinic sample to ensure the cohort studied were representative of a general TMD clinic population.

6.4.1 Age distribution

The mean age 32.3years (range 16-55years) concurs with the age distribution of patients previously reported in TMJ clinic populations.

Patients with TMD have frequently been reported to be within the ages of 19-44 years (Helkimo,1974, Von Korff et al,1988): 25-54 years (Dworkin et al,1990, Goulet et al,1995, List et al,1999). Feinmann and Harris 1984a, indicated the condition to be most commonly experienced in the third decade of life and this was again reiterated in more recent studies (Harrison et al,1997, Madland,2000, Truelove et al, 2005).

Interestingly, TMD affects a younger age group than those experiencing other chronic idiopathic orofacial pains which normally effects those with a mean age of 50 years, (Feinmann and Harris,1984a)

The age distribution for chronic TMD is also clearly lower than that found in other chronic muscular, skeletal or structural pain conditions of the body, which generally increase with age,(Anderson et al,1993, Ektor-Anderson et al,1993). It is descrbed as a condition of young and middle aged adults rather than children or the elderly, notably females of reproductive age,(Le Resche,1997).The reason for the unusual age distribution may become more apparent when the aetiology of the condition has become more clearly established.

6.4.2 Gender distribution

The ratio of 24% males to 76% females is again consistent with previous studies. This is clearly similar to the 75% of females reported by Bell,1989.

Overall symptom levels in non patient adults were almost equally distributed amongst males and females in early studies but are now believed to be in the ratio of 2:1 females:males,(Dworkin et al, 1990,Lipton et al,1993, Goulet et al,1995,Magnusson et al,2000) Meanwhile, presentation to a clinical environment is of the ratio of 3:1, 9:1 females to males (Levitt and McKinney,1994);3:1,4:1, (Dworkin and Le Resch,1993). Females generally seeking treatment for TMD three times more frequently than males,(Kultti et al,1998).

It has been suggested the high proportion of females seeking treatment may be due to greater health awareness amongst females (Randolph et al, 1990); or that women seek health care for pain more frequently than men (Le Resche,2001). Recent findings suggest cumulative exposure to females reproductive hormones may also be associated with onset of TMD in females,(LeResche et al,2005).

The over representation of female attendance at pain clinics may have a biological basis related to oestrogen dependent mediated analgesia, (Mogil et al1993).

Gender differences in pain response include increased genomic expression of c-fos in the hippocampal neurons in response to persistent nociceptive stimulation, (Aloisi et al,1996). Guilbaud et al, 1996, reported pain threshold variations with time in females but not males with decreased responsiveness of females to nonsteroidal antiinflamatory drugs over time,(Walker and Carmody,1996).Where the intensity of pain rather than severity of the pathological process relates to treatment need , different gender related pain signal processing may therefore result in altered perception and reaction to pain (Lavelle,2002, Bradburg,2003).

Interestingly, the small number of men attending clinics were recently found to have more difficulty than females in jaw opening and masticatory muscle problems, (Johansson, 2003).

6.4.3 Source of referrals

The majority were from GDP's (84%) following the postal request of patients.

6.4.4 Socio-economic status

The socioeconomic distribution revealed increased involvement of semi-professional (Class II) and non-professional clerical (ClassIIIi) and decreased involvement of semi-skilled (Class IV) and unskilled (Class V).This reflects the similar clinical findings of Harrison et al,1997 and Truelove et al, 2005. Epidemiological studies do not show evidence that TMD is less prevalent in the lower social classes (Crook et al,1984). The National Health Service (NHS) ensures inclusive access to health care for all social classes. Thomas et al,1997, however, suggests there appears to be an unwillingness to attend primary dental care partly due to lack of local NHS dentists. This may have consequently restricted the direct

referral path from the GDP due to possible decreased attendance of lower social classes. However, financial and time constraints may influence participation in clinical trials. The cost of travel into central London, time off work for hospital attendance or family care commitments may inadvertently exclude social classes IV and V. There was no reimbursement of travel expenses or financial incentive for taking part in the trial programme.

Length of hospital appointments, completion of questionnaires or poor understanding of written English may also have discouraged certain patients from trial participation.

Interestingly, Class VI, defined as economically inactive and comprised of the unemployed, students and housewives constitutes 32% of those participating in the study. This might suggest time is an important factor if one considers these individuals may have more time to attend appointments.

6.4.5 Employment status

66.8% of patients were employed, illustrating that a substantial proportion of individuals were prepared to take time of work to attend appointments.

6.4.6 Summary of demographics

The demographic features of the clinic population were comparable to previous TMD study cohorts. It is hoped results of the RCT will therefore be relevant and generalisable to most TMD clinic environments.

Since the randomisation procedure was blocked but unstratified, all demographic variables were compared between groups. This demonstrated an even and non-significant distribution of characteristics between groups.

6.5 Clinical features of the TMD study group

Hypothesis (3)

The duration, character and location of TMD pain described are typical of a patient population seen within a secondary or tertiary TMJ clinic.

6.5.1 Clinical history – TMJ symptoms:

These were recorded on a standardised clinical questionnaire (Appendix 8)

6.5.1.1 Pain duration

The mean duration of pain was 3 years (range 3months – 32 years). Interestingly, this is consistent with studies in the TMD clinic environment, (Madland ,2000, Truelove et al,2005).However, considering the intention of the study was to focus on patients with no previous TMJ treatment , it might have been assumed the length of pain experienced may have been considerably less than three years, perhaps nearer to the three to six months range that first classifies pain as chronic.

The remitting nature of pain or gradual worsening of symptoms may account for the delay in seeking treatment, (Dworkin and Le Reshe,1999 and Rammelsburg et al,2003).

This delay in treatment seeking may however have allowed the establishment of a central 'wind-up' process, neural plasticity and learned pain behaviour and coping mechanism which is already therefore difficult to deconstruct. It makes sense to theorise the sooner pain can be 'tackled' in its earlier stages the sooner the pain can be resolved without the temporal factor allowing for alterations to pain pathways and learned psychosocial behaviour.

6.5.1.2 Character and site of pain

The character of the pain was predominantly described as a dull ache (64%) and or discomfort (54.8%), most frequently unilateral (72%).

Location and character of pain were crucial to the diagnostic inclusion for the study. TMJ arthralgia with or without myalgia , internal disc derangement or limitation in mouth opening were a prerequisite for study inclusion. The majority of referring practitioners were aware of inclusion criteria and a diagnosis of TMJ pain had already been assigned to the patient but diagnosis had to be reconfirmed or established. Care was therefore taken to avoid technical terms or leading questions which might effect the patients response to this fundamental inquiry.

The patient was simply requested to describe and show the clinician the exact site of pain, asked to point with their finger to indicate the area on their head. The site of pain was transcribed by the clinician to a drawing of the face and shown to the patient who confirmed the location. The clinician then paraphrased the findings for final confirmation. For example, " a constant, dull ache just in front of the right ear, extending into the temple (or side of the head) and down into the jaw muscle", once more pointing to the sites indicated.

A diagram as a useful tool to indicate site of pain has previously been advocated in chronic facial and TMD pain (Harris ,1984, Orhbach,1995, Madland,2001). The drawing assists in restricting pain description to the head and neck region particularly helpful for patients who begin by describing a vague 'total body pain'. It can also be useful in deciphering multiple facial pain diagnoses in patients who indicate various pains in several sites over the head and neck region.

6.5.1.3 Frequency of bouts

The majority of patients reported constant pain but to confirm this finding; length, frequency of bouts and pain free intervals were also queried. In certain situations, patients described severe, sharp episodes of pain superimposed upon a continuous or frequent dull ache, a finding previously reported in TMD populations.

6.5.1.4 Diurnal variation

Daily patterns of pain correspond to previous TMD findings in which pain is reported to be worst in the morning, 45% (113/250) (Orhbach,1995). Whether this relates to a nocturnal bruxism habit remains a controversial issue. Only 20% (49/250) of patients believed they had a bruxism habit although 53% (133/250) reported a sensation of disturbed occlusal comfort.

6.5.1.5 Altered sleep patterns

Sleep disturbance and prevention were recorded in nearly half the study subjects. This may be a consequence of psychological issues, depression, anxiety or worry, other chronic pains or medical conditions, young families with babies particularly in the age group under investigation and environmental noise pollution in central London. Such factors cannot be controlled, but to clarify this issue the patient was asked to report sleep problems specifically related to TMJ pain. This still indicated prevention and disturbance of sleep with early morning waking, factors frequently also associated with depression.

A recent study suggests 65% of adults in the UK are chronically sleep deprived, working longer hours and sleeping fewer hours than a decade ago, (www.bbc\health,2004).

The issue of restorative sleep will be re-examined in more detail during the reporting of the three month study results.

6.5.1.6 Precipitating and provoking factors

The identification of initiating and perpetuating factors in aiding diagnosis and treatment for TMD, even in the absence of poorly defined biological mechanisms, was stressed by Drangsholt and Le Resche,1999. Longtitudinal population based studies are obviously more appropriate to gain such information but data from this study was nonetheless recorded.

The patient attributed the initiating factor for pain onset to be: unknown cause (27%), following dental treatment (restorative, surgical or orthodontic)(26%), infection(24%) physical trauma (16%) and emotional trauma (3%).The high incidence of reported onset following dental treatment may relate to extensive or prolonged mouth opening, but has not as yet been examined in prospective studies. Huang et al, 2002, however, does suggest removal of third molars to be a possible risk factor for TMD and hypothesise that extensive mouth opening, application of force to the mandible whilst removing teeth and general anaesthesia with consequent reduction in protective jaw mechanisms may result in trauma to the TMJ and musculature. Further prospective research is required to establish whether there is indeed a causal link.

The unusual association of onset to infection reported by patients, might either suggest they were trying to attribute a physical cause for the pain or that we are missing an as yet unidentified pathological, aetiological agent. However, it is important to note that the highest number of patients reported no obvious initiating factor.

Movements of the jaw, notably chewing (77%), yawning (76%) and biting (66%) were clearly aggravating factors for TMD as expected,(Le Resche et al, 1999, Leeson et al,2000). Slightly less frequently reported factors included emotional tension (54%), talking (32%) and cold weather (29%).

Interestingly, although patients did not necessarily attribute the initiation of pain to emotional trauma, over half were aware of an association between stress and anxiety in the aggravation of pain. This may, to some extent result from being confronted by a series of pain related psychosocial questionnaires in the waiting area, prior to the clinical assessment, causing the patient to reflect on emotional issues.

Talking was affecting pain in a third of individuals, an obvious cause for concern amongst patients.

Cold weather was also an important factor to consider since this may have an indirect influence on recorded pain levels rising, during the winter months of the study. Seasonal variation could therefore be considered a possible confounding factor in the study.

6.5.1.7 Relieving factors

Analgesics had been taken for TMD pain by over half the study sample in the past, in an attempt to alleviate pain. Other standard techniques employed had included resting the jaw (44%), pressure (38%) and application of warmth to the jaw (24%).

6.5.1.8 Recurrent chronic pains

There was a high proportion of concomitant headache (61%),neck ache (50%) and backache (48%) reported by the study participants. There were lower reports of migraine (33%), abdominal pain (30%), pruritis (22%) and chest pain(16%).Results

are consistent with those studying other chronic facial pain and TMD samples where a significant percentage of patients report other chronic pains, (Feinmann et al,1984, Le Resche et al,1987,Harrison et al,1997).

Concern arises as to whether co-morbid pain conditions impact on the patients reporting of pain, not only clinically but with regard to self report questionnaire responses relating to pain behaviour and psychosocial issues. Le Resche and von Korff, 2005, address the topic of co-morbidity, indicating the impracticality of excluding individuals with co-morbid pain conditions when a significant percentage of those with TMD are known to have other chronic pains notably headache and backache. The relationship between headache and TMD has led to speculation that the two conditions represent a spectrum of related conditions or share associated risk factors,(Benoliel and Sharav,1998).

There is clear evidence indicating patients with TMD and multiple co-morbid pain conditions are more psychologically distressed,(Le Resche et al 1987, Dworkin et al,1990).In addition there appears to be a greater risk of developing long-term TMD pain related disability and persisitent pain in patients with multiple pain sites (John et al,2003, Rammelsburg et al,2003)

6.5.2 Clinical examination TMJ signs:

6.5.2.1 Extra oral examination

6.5.2.1.1 TMJ and associated musculature

Muscle pain and clicking were present in approximately half of individuals with limitation in mouth opening noted in 18%.

6.5.2.1.2 Interincisal mouth opening

The only true parametric measure, the mean score on maximal, non painful, unassisted interinciscal mouth opening was 38.9mm (+/-9.35) .Only a small percentage of individuals exhibited deviation of the mandible on jaw opening.

6.5.2.2 Intra oral examination

6.5.2.2.1 Soft tissues – tongue, buccal and lingual mucosa.

On examination, ridging of the buccal mucosa was evident in over half the study cohort suggestive of a clenching or bruxism habit. Ridging or a scalloped margin of the tongue was less frequently recorded (12%).

6.5.2.2.2 Occlusion

The majority of cases were either Class I (39%) or Class IIi (38%). 32% had no missing posterior teeth but 32% had 4 missing posterior teeth and 10% greater than 5 missing posterior teeth. Interestingly, a large proportion of candidates (63%) had one or more missing wisdom teeth.

6.6 Pain and psychosocial self report questionnaires

6.6.1 Pain severity scores

Intensity of pain was measured using several different parameters incorporating both current and usual pain. The MPQ, PPI and VAS record current pain whilst MPQ reflects upon the usual description of pain.

The MPQ, PPI median scores were 2.00 (1.0,2.0) ,where 0=none, 5=excrutiating, most commonly indicating current levels of discomforting pain. The MPQ, VAS median scores were 2.9 (1.2,5.45) measured on a 10cm line. Although comparable

to previous TMD studies this appears relatively low. This is perhaps due to measurement of requested 'current' pain levels as opposed to recording levels during an episode of severe pain or accessing generalised level of pain. Constant pain is hence recorded with more accuracy than intermittent pain or pain of diurnal variation since there is no accounting for any temporal variation.

The MPI severity score is a composite score, rating level of pain at the present moment and severity over the last week. Perhaps a more versatile scale it therefore incorporates both the 'now' and 'recent' dimensions of pain.

The MPI severity median scores were 3.00 (1.83,4.00) ,scale (0-6), similar to those found in other TMD patient cohorts (Turk et al, 1993, Harrison et al, 1997).

6.6.2 Patients' perspective of pain-

Interference, life control and affective distress

The level of pain interference was a median 1.36(0.55,2.82) ,relatively low despite reported severity. However, affective distress experienced by the patient was calculated to be a median 3.33 (2.33,4.30) with life control 3.25(2.31,4.00).Pain was clearly causing the patients distress with a sense of lack of control in relation to their life and pain as previously reported in other facial pain studies (Harrison et al,1996).

6.6.3 Social support of family, spouse or friends

Supportive and solicitous responses of someone close to the patient , termed 'a significant other', had a median score of 3.33 (2.3,4.6) and 2.66(1.5,3.87) respectively. Distracting responses were lower at 1.75 (0.75,2.75) and fortunately punishing responses lowest at 1.0 (0,2.6). These scores indicate generally positive social support.Such findings are not necessarily mirrored in other groups of chronic

pain patients where longstanding pain may adversely affect social support (Williams et al, 1996, Newton-John,2002).

6.6.4 Activity level

Frequency of participation in household chores, activities away from home, social activities and general activity levels were recorded with median scores of 4.8 (3.6,5.6), 3.5 (2.75,4.25), 3.0(2.3,4.0), 3.38(2.75,3.9) respectively suggesting TMD patients are not particularly restricted or disabled by their pain. Only outdoor work median score 2.00(1.0,3.00) seemed slightly lower which might be related to those individuals who found cold weather an aggravating factor. Generally, good activity levels may be related to the site of TMD pain in comparison for example to back pain patients who report more difficulties in performing daily tasks,(Anderson,1999) Level of chronicity and depression may also influence activity levels and these patients were generally not clinically depressed.

6.6.5 Depression scores (BDI)

The median BDI depression scores were 7.00 (3.00,13.00) indicating the TMD patients studied were generally not depressed but within the normal population range. The percentage of patients with scores greater than 20, suggestive of clinical depression was only, 11 %, (26/237). This is lower compared to other chronic pain patient cohorts (Magni et al,1990) In this study, most patients were referred by a primary care practitioner, which may indicate patients had been less exposed to previous treatment intervention whereas tertiary pain referrals might be regarded as atypical in their presentation of high levels of depression and psychosocial dysfunction reflecting different clinic populations,(vonKorff and Simon,1996).

6.6.6 Illness attitudes (Kellner)

Disease phobia had a median score of 3.0(3.0,6.0) and hypochondriacal beliefs 3.0 (3.0,5.0) with a total score of 8.00 (6.00,11.00). Results suggest average scores, indicating the TMD patients studied generally had a normal range of illness attitude.

Having established the baseline recordings for the study cohort the next chapter deals with the treatment phase of the randomised controlled trial.

VII RESULTS

TREATMENT OUTCOME

7.0 THE RESEARCH STUDY, TREATMENT OUTCOME

Hypotheses (1a) and (1b)

(1a) An SSRI (fluoxetine;Prozac) in daily oral doses of 20-40mg is more effective than placebo in the treatment of patients with chronic TMD.

(1b) A combination of an SSRI (fluoxetine;Prozac) and a bite guard are equally effective to fluoxetine or bite guard alone in the treatment of chronic TMD.

7.0.1 Outcome measures

Efficacy of treatment, to prove or disprove the above hypotheses, were investigated using the primary and secondary outcome measures. These were recorded using the clinician recorded amelioration in clinical signs and symptoms, the self report numerical and verbal rating scales and the patient recorded pain and psychosocial questionnaires.

Recordings at baseline, with repeated measures during the treatment phase and or at the end of the trial period of three months were analysed. Both completers of treatment intention to treat analyses, for all those originally allocated to treatment and imputation analyses for missing data were performed and presented separately in graphical and tabular format. The results are presented in the following order:

7.0.2 Primary outcome measures summarised

Primary outcome measure (please see section 7.1)

Greater than 50% pain relief, was calculated as the primary outcome measure to determine treatment effect size and numbers needed to treat (NNT). These were calculated using the visual analogue scale VAS (10cm) of patient reported, current pain intensity.

7.0.3 Summary of secondary outcome measures

Secondary outcome measures (please see section 7.2)

7.0.3.1 Clinician recorded

Self report verbal rating scales (Non parametric) **(section 7.2.1)**

Amelioration in scores at four, eight and twelve weeks from baseline.

- Present pain intensity (Non / mild / moderate / severe) **(section 7.2.1.1)**
- Frequency scores (never / occasionally / often / always) **(section 7.2.1.2)**
- Severity scores (worse / in pain / improved / pain free) **(section 7.2.1.3)**
- Interference with life (Yes / No) **(section 7.2.1.4)**

Clinical signs and symptoms (section 7.2.2)

Amelioration at four, eight and twelve weeks form baseline.

- Interincisal mouth opening (in mm) (Parametric) **(section 7.2.2.1)**
- TMD signs and symptoms (Non parametric) **(section 7.2.2.2)**
- TMD character (Non parametric) **(section 7.2.2.3)**
- Chronic recurrent pains (Non parametric) **(section 7.2.2.4)**

7.0.3.2 Patient recorded

Pain and psycholosocial self report questionnaires (Non parametric) **(see 7.2.3)**

Amelioration in scores at treatment end, three months from baseline.

- MPI **(section 7.2.3.1)**
- MPQ **(section 7.2.3.2)**
- BDI **(section 7.2.3.3)**
- Kellner **(section 7.2.3.4)**

7.1 PRIMARY OUTCOME MEASURE

7.1.0 Primary outcome measure

In this study, the definition for target improvement, as specified in the protocol, was >25% pain relief. In the medical literature pain relief is frequently quoted as >50%. Consequently the power calculation for this trial was undertaken with the higher 50% percentage, so that both 50% and 25% pain relief could be investigated. The measure used to calculate the primary outcome measure was the VAS (visual analogue 10cm scale). Scores of >25% and >50% improvement at the end of the three months treatment were recorded for each therapeutic group in order to calculate the effect size with 95% confidence intervals and the Numbers needed to treat (NNT)

7.1.1 Measures used to calculate the effect size and NNT

The treatment effect size and 95% confidence intervals indicate whether the result is comparable with a clinically important effect, (Altman et al, 2001).

A favourable outcome in treatment response was recorded for all therapeutic groups. Improvement in >50% and >25% pain relief on the 10cm VAS was observed for each treatment group but there was no significant difference between groups, (tables 19, figures 31). A combination of an SSRI (fluoxetine:Prozac) and a bite guard therefore appear equally effective to fluoxetine or bite guard alone in the treatment of chronic TMD.

However, a significant difference was observed between SSRI and placebo at >50% pain relief. An effect size of 2.07 (CI 1.16-3.70) for the ITT, (N=201) and 1.84 (CI 1.05-3.24) for the completers analysis, (N=165).

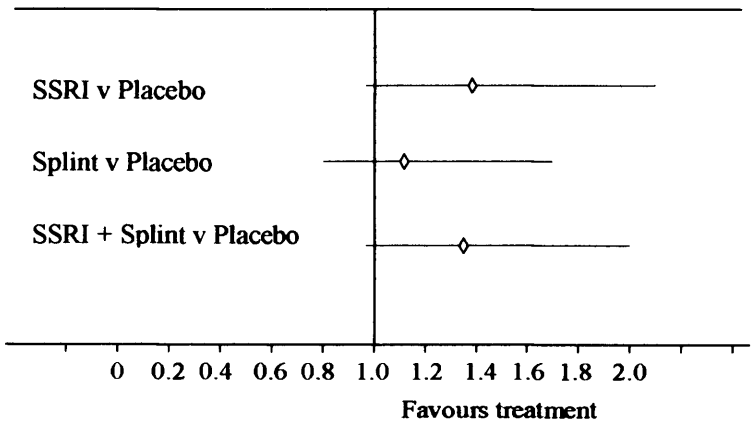
Tables 19a: Comparison of treatment groups at three months >25% improvement in pain (VAS), Intention to treat analysis (N=201)

Group	Treatment	>25% pain reduction VAS	<25% pain reduction VAS	Total
1	SSRI	31/49 (63%)	18/49 (37%)	49
2	Placebo	24/53 (45%)	29/53 (55%)	53
3	Splint	27/51 (53%)	24/51 (47%)	51
4	SSRI + Splint	30/48 (63%)	18/48 (37%)	48
Total		112	89	201

Table 19b: Treatment effect size and confidence intervals at three months >25% improvement in pain (VAS), Intention to treat analysis (N=201)

Treatment	(n/N)	Placebo (n/N)	Effect size (95% CI)
SSRI	31/49	24/53	1.40 (0.97-2.01)
Splint	27/51	24/53	1.17 (0.80-1.73)
SSRI + Splint	30/48	24/53	1.38 (0.96-2.00)

Figure 31a: Diagram illustrating treatment effect size and confidence intervals >25% improvement in pain (VAS), Intention to treat analysis (N=201), 3 months.



Analysing the data for >25% improvement, there is an overall favourable response to all therapies but confidence intervals, (table 21b) suggest the improvement is not significant in comparison to placebo treatment.

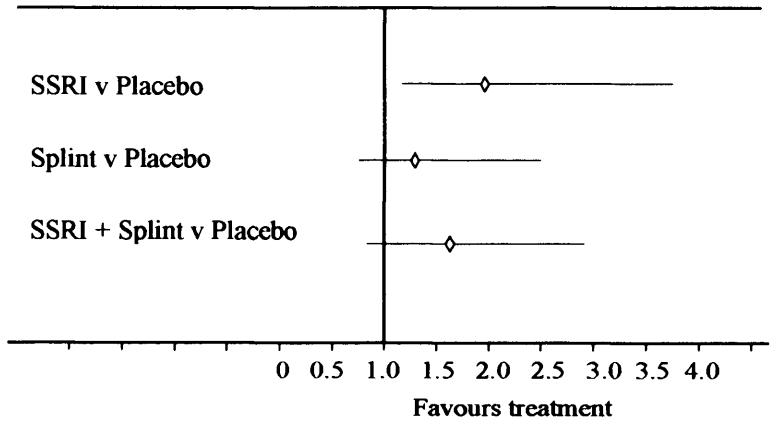
19c: Comparison of treatment groups at three months, >50% improvement in pain (VAS), Intention to treat analysis (N=201)

Group	Treatment	>50% pain reduction VAS	<50% pain reduction VAS	Total
1	SSRI	23/49 (47%)	26/49 (53%)	49
2	Placebo	12/53 (23%)	41/53 (77%)	53
3	Splint	15/51 (29%)	36/51 (71%)	51
4	SSRI Splint	17/48 (35%)	31/48 (65%)	48
Total		67	134	201

Tables 19d: Treatment effect size and confidence intervals at three months, >50% improvement in pain (VAS), Intention to treat analysis (N=201)

Treatment	(n/N)	Placebo (n/N)	Effect size (95% CI)
SSRI	23/49	12/53	* 2.07 (1.16-3.70)
Splint	15/51	12/53	1.29 (0.68-2.50)
SSRI + Splint	17/48	12/53	1.56 (0.84-2.93)

Figure 31b: Diagram illustrating treatment effect size and confidence intervals >50% improvement in pain (VAS), Intention to treat analysis (N=201), 3 months.



Analysing the data for >50% improvement, not only is there an overall favourable response amongst all therapeutic groups but confidence intervals, (table 21d) suggest the improvement for the SSRI group 2.07 (1.16-3.70) is significant in comparison to placebo. This suggests patients are twice as likely to develop > 50% reduction in pain with SSRI therapy compared to placebo.

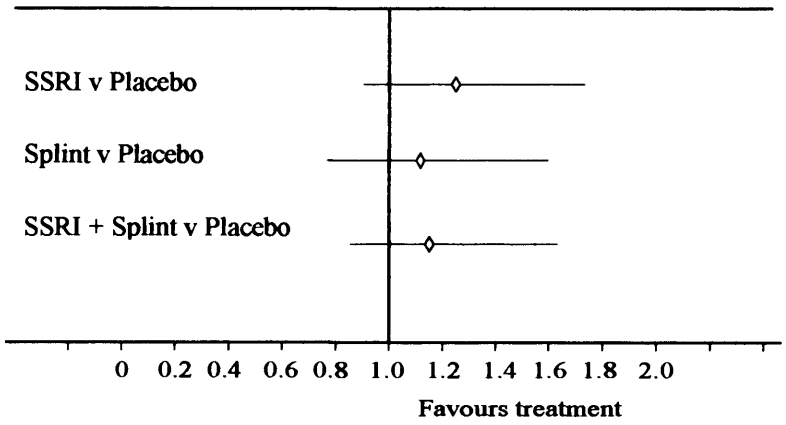
Table 19e: Comparison of treatment groups at three months >25% improvement in pain (VAS), Completers analysis (N=165)

Group	Treatment	>25% pain reduction VAS	<25% pain reduction VAS	Total
1	SSRI	26/38 (68%)	12/38 (32%)	38
2	Placebo	23/42 (55%)	19/42 (45%)	42
3	Bite guard	24/40 (60%)	16/40 (40%)	40
4	SSRI and bite guard	28/45 (62%)	17/45 (38%)	45
Total		101	64	165

Tables 19f: Treatment effect size and confidence intervals at three months, >25% improvement in pain (VAS), Completers analysis (N=165)

Treatment	(n/N)	Placebo (n/N)	Odds Ratio (95% CI)
SSRI	26/38	23/42	1.25 (0.88-1.77)
Splint	24/40	23/42	1.10 (0.75-1.60)
SSRI + Splint	28/45	23/42	1.14 (0.80-1.62)

Figure 31c: Diagram illustrating treatment effect size and confidence intervals >25% improvement in pain (VAS), Completers analysis (N=165), 3 months.



Analysing the data for >25% improvement, again there is an overall favourable response to all therapies but confidence intervals, (table 21e) again suggest the improvement is not significant in comparison to placebo treatment.

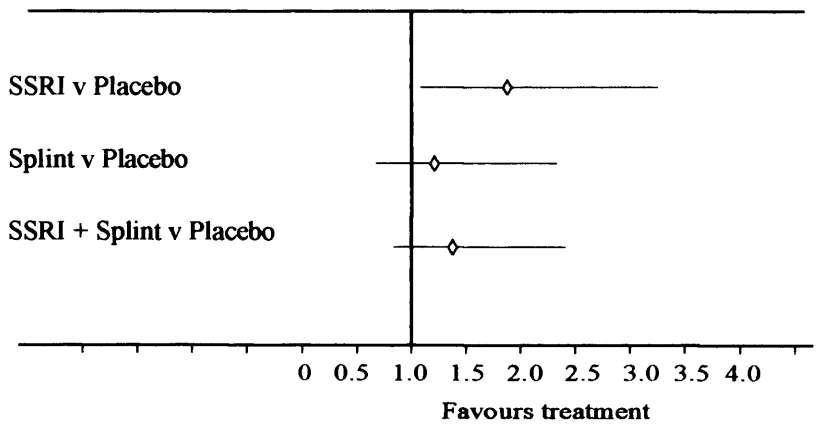
Tables 19g: Comparison of treatment groups at three months, >50% improvement in pain (VAS), Completers analysis (N=165)

Group	Treatment	>50% pain reduction VAS	<50% pain reduction VAS	Total
1	SSRI	20/38 (53%)	18/38 (47%)	38
2	Placebo	12/42 (29%)	30/42 (71%)	42
3	Bite guard	14/40 (35%)	26/40 (65%)	40
4	SSRI and bite guard	17/45 (38%)	28/45 (62%)	45
Total		63	102	165

Tables 19h: Treatment effect size and confidence intervals at three months, >50% improvement in pain (VAS), Completers analysis (N=165)

Treatment	(n/N)	Placebo (n/N)	Odds Ratio (95% CI)
SSRI	20/38	12/42	*1.84 (1.05-3.24)
Splint	14/40	12/42	1.23 (0.65-2.32)
SSRI + Splint	17/45	12/42	1.32 (0.72-2.43)

Figure 31d: Diagram illustrating treatment effect size and confidence intervals >50% improvement in pain (VAS), Completers analysis (N=165), 3 months.



Once again, analysing the data for >50% improvement, not only is there is an overall favourable response amongst all therapeutic groups but confidence intervals, (table 21d) suggest the improvement for the SSRI group 1.84 (1.05-3.24) is significant in comparison to placebo. This suggests patients are almost twice as likely to benefit from > 50% reduction in pain with SSRI therapy compared to placebo.

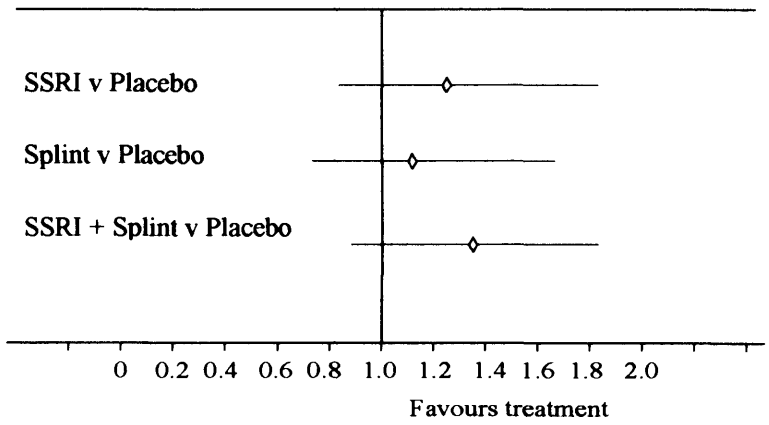
Table 19i: Comparison of treatment groups at three months >25% improvement in pain (VAS), Imputation analysis (N=250)

Group	Treatment	>25% pain reduction VAS	<25% pain reduction VAS	Total
1	SSRI	31/63 (49%)	32/63 (51%)	63
2	Placebo	25/63 (40%)	38/63 (60%)	63
3	Bite guard	27/62 (44%)	35/62 (56%)	62
4	SSRI and bite guard	30/62 (48%)	32/62 (52%)	62
Total		68	182	250

Tables 19j: Treatment effect size and confidence intervals at three months, >25% improvement in pain (VAS), Imputation analysis (N=250)

Treatment	(n/N)	Placebo (n/N)	Odds Ratio (95% CI)
SSRI	31/63	25/63	1.24 (0.84-1.84)
Splint	27/62	25/63	1.10 (0.72-1.66)
SSRI + Splint	30/62	25/63	1.22 (0.82-1.82)

Figure 31e: Diagram illustrating treatment effect size and confidence intervals >25% improvement in pain (VAS), Imputation analysis (N=250), 3 months.



Even utilising the more rigorous imputation analysis, the data for >25% improvement reveals an overall favourable response to all therapies but confidence intervals, (table 21e) again suggest the improvement is not significant in comparison to placebo treatment.

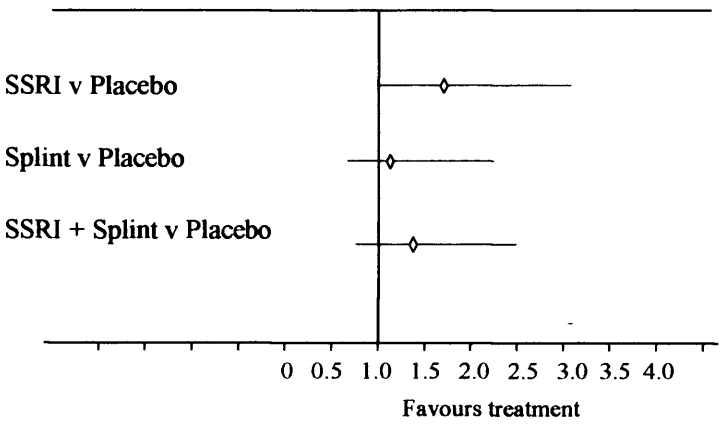
Tables 19k: Comparison of treatment groups at three months, >50% improvement in pain (VAS), Imputation analysis (N=250)

Group	Treatment	>50% pain reduction VAS	<50% pain reduction VAS	Total
1	SSRI	31/63 (49%)	32/63 (51%)	63
2	Placebo	25/63 (40%)	38/63 (60%)	63
3	Bite guard	27/62 (44%)	35/62 (56%)	62
4	SSRI and bite guard	30/62 (48%)	32/62 (52%)	62
Total		68	182	250

Tables 19l: Treatment effect size and confidence intervals at three months, >50% improvement in pain (VAS), Imputation analysis (N=250)

Treatment	(n/N)	Placebo (n/N)	Odds Ratio (95% CI)
SSRI	31/63	25/63	1.77 (0.99-3.17)
Splint	27/62	25/63	1.17 (0.61-2.26)
SSRI + Splint	30/62	25/63	1.33 (0.71-2.50)

Figure 31f: Diagram illustrating treatment effect size and confidence intervals >50% improvement in pain (VAS), Imputation analysis (N=250), 3 months.



Analysing the data for >50% improvement, using the imputation analysis suggests an overall favourable response to therapies but confidence intervals, (table 21e) suggest the improvement is not significant in comparison to placebo treatment.

Tables 19m: A comparison of treatment effect size and confidence intervals >25% improvement in pain (VAS), Intention to treat analysis (N=201), 3 months

Treatment	(n/N)	Treatment	(n/N)	Odds Ratio (95% CI)
SSRI	31/49	Splint	27/51	1.53 (0.69-3.41)
SSRI	31/49	SSRI + Splint	30/48	1.03 (0.45-2.36)
SSRI + Splint	30/48	Splint	27/51	1.18 (0.84-1.66)

Figure 31g: Diagram illustrating treatment effect size and confidence intervals >25% improvement in pain (VAS), Intention to treat analysis (N=201), 3 months

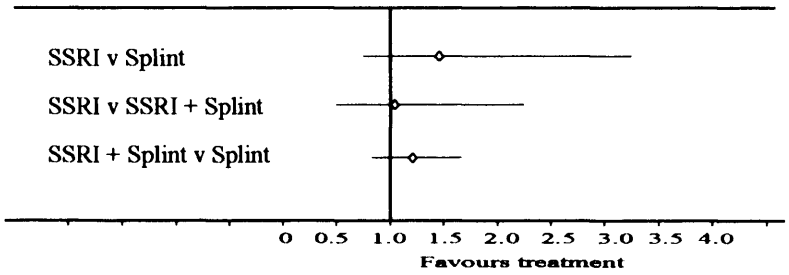
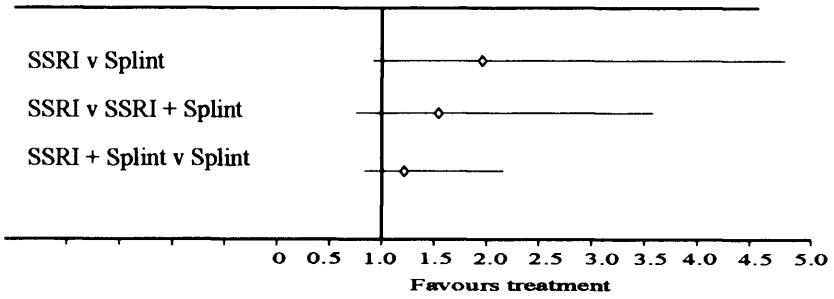


Table 19n: A comparison of treatment effect size and confidence intervals >50% improvement in pain (VAS), Intention to treat analysis (N=201), 3 months.

Treatment	(n/N)	Treatment	(n/N)	Odds Ratio (95% CI)
SSRI	23/49	Splint	15/51	2.12 (0.93-4.84)
SSRI	23/49	SSRI + Splint	17/48	1.61 (0.71-3.65)
SSRI + Splint	17/48	Splint	15/51	1.20 (0.68-2.13)

Figure 31h: Diagram illustrating treatment effect size and confidence intervals >50% improvement in pain (VAS), Intention to treat analysis (N=201), 3 months.



There is no significant difference in treatment effect for >25% or >50% improvement in pain, between groups.

Tables 19o: A comparison of treatment effect size and confidence intervals >25% improvement in pain (VAS), Completers analysis (N=165), 3 months

Treatment	(n/N)	Treatment	(n/N)	Odds Ratio (95% CI)
SSRI	26/38	Splint	24/40	1.44 (0.57-3.67)
SSRI	26/38	SSRI + Splint	28/45	1.32 (0.53-3.27)
SSRI + Splint	28/45	Splint	24/40	1.04 (0.74-1.46)

Figure 31i: Diagram illustrating treatment effect size and confidence intervals >25% improvement in pain (VAS), Completers analysis (N=165), 3 months.

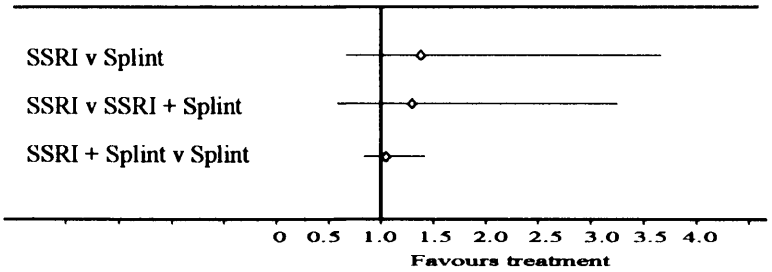
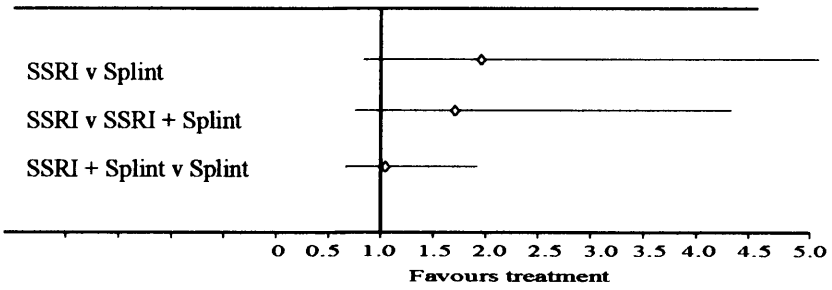


Table 19p: A comparison of treatment effect size and confidence intervals >50% improvement in pain (VAS), Completers (N=165), 3 months.

Treatment	(n/N)	Treatment	(n/N)	Odds Ratio (95% CI)
SSRI	20/38	Splint	14/40	2.08 (0.83-5.13)
SSRI	20/48	SSRI+Splint	17/45	1.83 (0.76-4.40)
SSRI + Splint	17/45	Splint	14/40	1.08 (0.61-1.90)

Figure 31j: Diagram illustrating treatment effect size and confidence intervals >50% improvement in pain (VAS), Completers analysis (N=165), 3 months.



There is no significant difference in treatment effect for >25% or >50% improvement in pain, between groups.

Tables 19q: A comparison of treatment effect size and confidence intervals >25% improvement in pain (VAS), Imputation analysis (N=250), 3 months.

Treatment	(n/N)	Treatment	(n/N)	Odds Ratio (95% CI)
SSRI	31/63	Splint	27/62	1.26 (0.62-2.54)
SSRI	31/63	SSRI + Splint	30/62	1.03 (0.51-2.08)
SSRI + Splint	30/62	Splint	27/62	1.11 (0.76-1.63)

Figure 31k: Diagram illustrating treatment effect size and confidence intervals >25% improvement in pain (VAS), Completers analysis (N=250), 3 months.

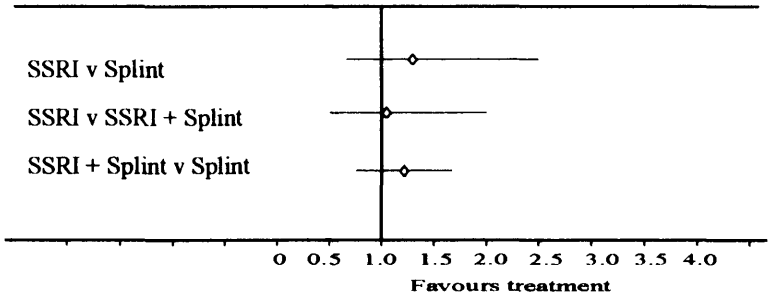
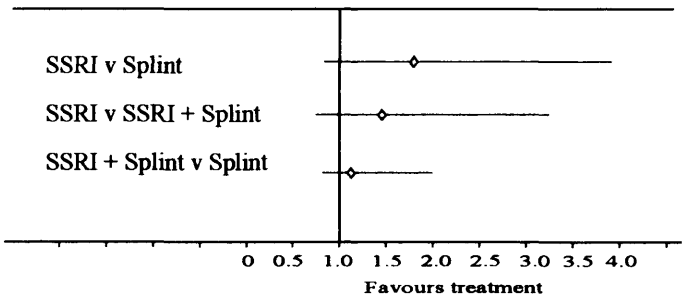


Table 19r: A comparison of treatment effect size and confidence intervals >50% improvement in pain (VAS), Completers (N=250), 3 months.

Treatment	(n/N)	Treatment	(n/N)	Odds Ratio (95% CI)
SSRI	23/63	Splint	15/62	1.80 (0.83-3.91)
SSRI	23/63	SSRI+Splint	17/62	1.52 (0.71-3.25)
SSRI + Splint	17/62	Splint	15/63	1.13 (0.62-2.06)

Figure 31l: Diagram illustrating treatment effect size and confidence intervals >50% improvement in pain (VAS), Imputation analysis (N=250), 3 months.



Once again, there is no significant difference in treatment effect for >25% or >50% improvement in pain, between groups.

7.1.2 Numbers needed to treat analysis (NNT)

	Placebo (control)	Active treatment
Total number of patients	N_{cont}	N_{act}
Clinical endpoint, improvement achieved	Imp_{cont}	Imp_{act}

$$NNT = \frac{1}{(Imp_{act} / N_{act}) - (Imp_{cont} / N_{cont})} = \frac{1}{ARR}$$

Using the data from tables 19a,b,c,d,e,f the above calculation was used to determine the NNT for each form of therapy. The results presented on the following page, (7.1.1.1),(table 20a,b) are for the ITT analysis,(N=201). These results suggest that for every 100 TMD patients, >50% pain relief could be achieved in (100/4.1) 24 patients with fluoxetine, (100/14.8) 7 patients with a bite guard and (100/7.8) 13 patients with fluoxetine and biteguard. For every 100 TMD patients >25% pain relief could be achieved in (100/5.6) 18 patients with fluoxetine, (100/13.1) 8 patients with a bite guard and (100/5.8) 17 patients with both fluoxetine and biteguard.

Data from the imputation analysis,(N=250), is illustrated in section (7.1.1.2,(table 20c,d). These results suggest that for every 100 TMD patients, >50% pain relief could be achieved in (100/6.3) 16 patients with fluoxetine, (100/28.1) 4 patients with a bite guard and (100/14.7) 7 patients with fluoxetine and biteguard. For every 100 TMD patients >25% pain relief could be achieved in (100/10.5) 9 patients with fluoxetine, (100/25.9) 4 patients with a bite guard and (100/11.5) 9 patients with both fluoxetine and biteguard.

A completers analysis,(N=165), is also illustrated in section (7.1.1.3,(table 20e,f). These results suggest that for every 100 TMD patients, >50% pain relief could be achieved in (100/4.2) 24 patients with fluoxetine, (100/15.6) 6 patients with a bite guard and (100/10.9) 9 patients with fluoxetine and biteguard. For every 100 TMD patients >25% pain relief could be achieved in (100/7.3) 14 patients with fluoxetine, (100/19.09) 5 patients with a bite guard and (100/13.4) 7 patients with both fluoxetine and biteguard.

7.1.1.1 NNT (Intention to treat analysis)

Table 20a: NNT: Analysing all those who commenced treatment (N=201)
Improvement VAS (10cm line) (pain relief >50%) three months study phase.

Fluoxetine

$$NNT = \frac{1}{(23/49) - (12/53)} = 4.1 \quad 95\%CI\ (2.5\text{-}17.2)$$

Bite guard

$$NNT = \frac{1}{(15/51) - (12/53)} = 14.8 \quad (4.3\text{-}\infty)$$

Fluoxetine and biteguard

$$NNT = \frac{1}{(17/48) - (12/53)} = 7.8 \quad (3.4\text{-}20.7)$$

Table 20b: NNT: Analysing all those who commenced treatment (N=201)
Improvement VAS (10cm line)(pain relief >25%) three month study phase

Fluoxetine

$$NNT = \frac{1}{(31/49) - (24/53)} = 5.6 \quad (2.8\text{-}76.8)$$

Bite guard

$$NNT = \frac{1}{(27/51) - (24/53)} = 13.1 \quad (3.8\text{-}\infty)$$

Fluoxetine and biteguard

$$NNT = \frac{1}{(30/48) - (24/53)} = 5.8 \quad (2.9\text{-}46.1)$$

7.1.1.2 NNT (Completers analysis) All those who completed treatment

Table 20c: NNT: Analysing all those randomised to the study (N=165)
Improvement VAS (10cm line) (pain relief >50%) three months study phase.

Fluoxetine

$$\text{NNT} = \frac{1}{(20/38) - (12/42)} = 4.2 \quad 95\%\text{CI } (2.34\text{-}38.70)$$

Bite guard

$$\text{NNT} = \frac{1}{(14/40) - (12/42)} = 15.6 \quad (3.90\text{-}\infty)$$

Fluoxetine and biteguard

$$\text{NNT} = \frac{1}{(17/45) - (12/42)} = 10.9 \quad (3.61\text{-}\infty)$$

Table 20d: NNT: Analysing all those completing treatment (N=165)
Improvement VAS (10cm line) (pain relief >25%) three months study phase.

Fluoxetine

$$\text{NNT} = \frac{1}{(26/38) - (23/42)} = 7.3 \quad 95\%\text{CI } (3.03\text{-}13.30)$$

Bite guard

$$\text{NNT} = \frac{1}{(24/40) - (23/42)} = 19.1 \quad (3.94\text{-}\infty)$$

Fluoxetine and biteguard

$$\text{NNT} = \frac{1}{(28/45) - (23/42)} = 13.4 \quad (3.71\text{-}\infty)$$

7.1.1.2 NNT (Imputation analysis) All those randomised to the study

Table 20e: NNT: Analysing all those randomised to the study (N=250)
Improvement VAS (10cm line) (pain relief >50%) three months study phase.

Fluoxetine

$$NNT = \frac{1}{(23/63) - (13/63)} = 6.3 \quad 95\%CI\ (3.26\text{-}\infty)$$

Bite guard

$$NNT = \frac{1}{(15/62) - (13/63)} = 28.1 \quad (5.54\text{-}\infty)$$

Fluoxetine and biteguard

$$NNT = \frac{1}{(17/62) - (13/63)} = 14.7 \quad (4.66\text{-}\infty)$$

Table 20f: NNT: Analysing all those randomised to the study (N=250)
Improvement VAS (10cm line) (pain relief >25%) three months study phase.

Fluoxetine

$$NNT = \frac{1}{(31/63) - (25/63)} = 10.5 \quad (3.86\text{-}13.08)$$

Bite guard

$$NNT = \frac{1}{(27/62) - (25/63)} = 25.9 \quad (4.88\text{-}\infty)$$

Fluoxetine and biteguard

$$NNT = \frac{1}{(30/62) - (25/63)} = 11.5 \quad (3.97\text{-}11.78)$$

7.1.3 Visual analogue scale (VAS) summary

VAS a numerical rating scale, used in the analyses of >50% and >25% improvement for the NNT, was measured at baseline, four, eight and twelve weeks. Detailed in tables 21a, b, c, d, there is clearly a significant reduction in level of pain for all treatment groups ($p<0.001$), as recorded on the 10cm VAS. This was observed both in the imputation analysis (N=250) (last score brought forward for any missing data values) and in the pragmatic analysis (N=165) (only analysing patients with complete data records). Graphically this is illustrated in figures 32 a,b as an overall reduction in pain scores. The same response was also observed in the intention to treat analysis (N=201), table 21e.

Both parametric and nonparametric analysis was undertaken for completeness and both confirmed identical findings.

In the parametric completers analysis using repeated measures ANOVA and the Greenhouse-Geisser correction, $F(2.37, 383.08)=59.07, P<0.001$ showing a significantly linear or straight line trend $p<0.001$ as illustrated in table 21c,fig 32b.

Similarly in the pragmatic, imputation analysis $F(2.17,540.40)=57.85, p<0.001$ with a significantly linear trend,$p<0.001$, table 21d, fig 32b.

In the non parametric intra group analysis, Wilcoxon signed rank test showed a significant improvement during the course of the studying in the completers and imputation analysis, $p<0.001$, consistent amongst all groups.

In all inter group analyses there was no significant difference overall in outcome measures between the four groups.

In the completers analysis VAS improved by 2.5cm from a mean 5.77cm(SD2.29) at baseline to 3.25cm(SD 2.41) at 12 weeks a significant reduction in pain for all

groups (n=165).Amongst individual groups; group 1 (n=38) showed improvement of 2.8cm from 5.89cm(SD2.30) to 2.75cm(SD2.48); group 2 (n=42) 2.5cm from 5.97cm(SD2.33) to 3.42cm(SD2.32); group 3 (n=40),2.4cm from 5.56cm(SD2.18) to 3.19cm(SD2.22); group4 (n=45) 2.0cm from 5.68cm(SD2.39) to3.56cm(SD2.61).

Similary this improvement is observed in the imputation analysis. All groups combined (n=250) showing a reduction in pain of 1.7cm for 5.77cm(SD2.29) to 4.06cm (SD2.59), whilst in separate groups;group 1(n=63) 2.1cm from 5.89cm(SD2.30) to 3.80cm(SD2.81); group 2(n=63) 1.7cm from 5.97cm(SD2.33) to 4.31cm(SD2.46);group 3(n=62) 1.5cm from 5.56cm(SD2.18) to 4.02cm(SD2.39); group 4(n=62) 1.6cm from 5.68cm(SD2.39) to 4.11cm(SD2.62).

Median scores showed a similar trend, for the completers analysis combined groups (n=165) pain scores decreased by 2.7cm, from 5.55(4.68-7.60) to 2.90(0.90-4.90) whilst in separate groups;group 1 (n=38) by 3.5cm, from 6.30(500-7.50) to 2.80(0-4.90)group 2 (n=42) by 2.7cm, from 6.20(5.00-7.70) to 3.55(0.98-4.93)
group 3 (n=40) by 2.1cm, from 5.0(3.70-7.60) to 2.90(0.90-4.90)
group 4 (n=45) by 1.4cm, from 5.20(4.80-7.70) to 3.85(1.05-5.23)

For the imputation analysis median pain scores decreased in the combined groups (n=250) by 1.1cm, from 5.55(4.68-7.60) to 4.45(2.70-5.83) whilst in the groups;
group 1 (n=63) by 2.7cm, from 6.30(4.90-7.50) to 3.60(0.80-6.30)
group 2 (n=63) by 1.4cm, from 6.20(5.00-7.70) to 4.80(2.80-5.90)
group 3 (n=62) by 1.3cm, from 5.00(3.70-7.60) to 3.75(2.80-5.23)
group 4 (n=62) by 0.5cm, from 5.20(4.75-7.70) to 4.70(2.38-5.45)

Table 21a: VAS (visual analogue scale,10cm line) A comparison of mean scores (+/-SD, standard deviation) Pragmatic, Completers analysis.(N=165)

Week	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups (1-way ANOVA)
0	n=250 5.77 (2.29)	n=63 5.89 (2.30)	n=63 5.97 (2.33)	n=62 5.56 (2.18)	n=62 5.68 (2.39)	**ns** p =0.74
4	n=191 4.30 (2.20) ***	n=47 4.06 (2.23) ** (p=0.001)	n=49 4.79 (2.34) ** (p=0.002)	n=47 4.22 (1.87) ***	n=48 4.10 (2.30) ***	**ns** p =0.33
8	n=178 3.88(2.43) ***	n=43 3.99 (2.58) ** (p=0.001)	n=47 4.21 (2.52) ***	n=43 3.62 (2.09) ***	n=45 3.68 (2.52) ***	**ns** p =0.63
12	n=165 3.25 (2.41) ***	n=38 2.75 (2.48) ***	n=42 3.43 (2.32) ***	n=40 3.19 (2.22) ***	n=45 3.56 (2.61) ***	**ns** p =0.45
	✱✱✱	✱✱✱	✱✱✱	✱✱✱	✱✱✱	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Repeated measures ANOVA P<0.0001✱✱✱ Paired sample t-test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : One-way ANOVA(not significant)

Table 21b: VAS (visual analogue scale,10cm line) . A comparison of mean scores (+/-SD)
Imputation analysis - Last score brought forward (N=250)

Week	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance between groups (1-way ANOVA)
0	5.77 (2.29)	5.89 (2.30)	5.97 (2.33)	5.56 (2.18)	5.68 (2.39)	**ns** p =0.74
4	4.69(2.23) ***	4.71 (2.46) ** (p=0.001)	4.94 (2.18) ** (p=0.002)	4.62 (2.04) ***	4.48 (2.25) ***	**ns** p =0.70
8	4.39 (2.44) ***	4.58 (2.67) ** (p=0.001)	4.53 (2.33) ***	4.26 (2.24) ***	4.20 (2.54) ***	**ns** p =0.77
12	4.06 (2.57) ***	3.80 (2.81) ***	4.31 (2.46) ***	4.02 (2.39) ***	4.11 (2.62) ***	**ns** p=0.74
	✱✱✱	✱✱✱	✱✱✱	✱✱✱	✱✱✱	

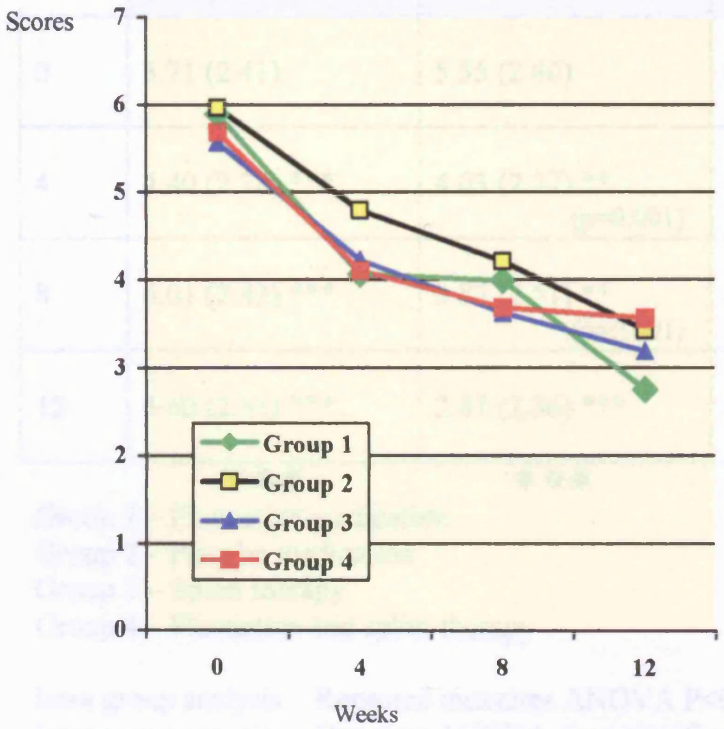
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Repeated measures ANOVA P<0.001✱✱✱ Paired sample t-test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : One-way ANOVA (not significant)

Figure 31 : A parametric comparison of completers analysis and imputation (last observation carried forward) analysis

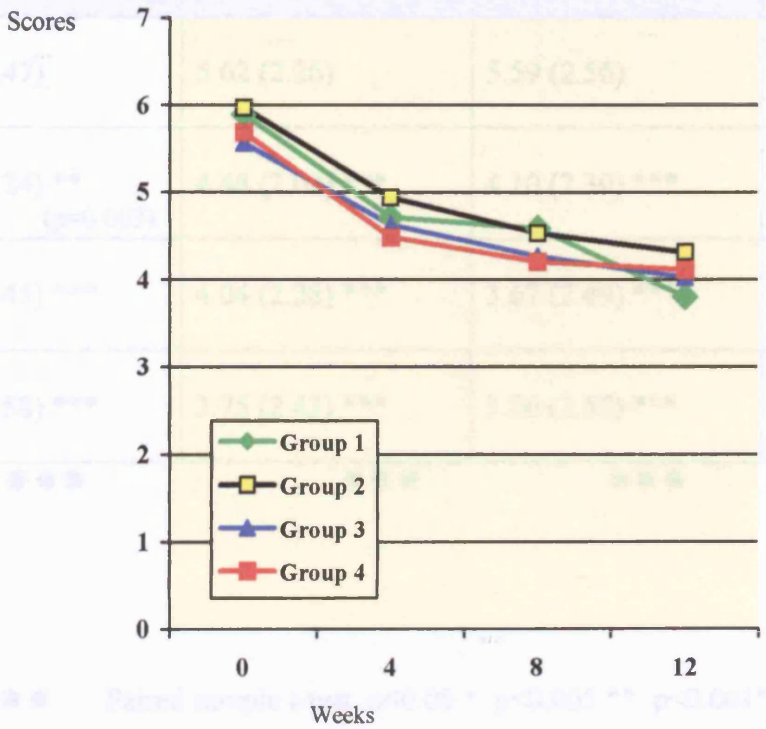
VAS (visual analogue scale) A comparison of mean scores

Completers analysis



VAS (visual analogue scale) A comparison of mean scores

Imputation analysis



Group 1 – Fluoxetine medication Group 3 – Splint therapy
Group 2 – placebo medication Group 4 – Fluoxetine and splint therapy

Table 21c: VAS (visual analogue scale,10cm line) . A comparison of mean scores (+/-SD)
Intention to treat analysis – (N=201)

Week	All groups (n=201)	Group 1 (n=49)	Group 2 (n=53)	Group 3 (n=51)	Group 4 (n=48)	Significance between groups (1-way ANOVA)
0	5.71 (2.41)	5.55 (2.40)	6.07 (2.47)	5.62 (2.26)	5.59 (2.56)	**ns** p =0.67
4	4.40 (2.24) ***	4.03 (2.27) ** (p=0.001)	4.95 (2.24) ** (p=0.003)	4.48 (2.08) ***	4.10 (2.30) ***	**ns** p =0.14
8	4.01 (2.43) ***	3.87 (2.51) ** (p=0.001)	4.42 (2.45) ***	4.04 (2.28) ***	3.67 (2.49) ***	**ns** p =0.46
12	3.60 (2.51) ***	2.87 (2.36) ***	4.18 (2.58) ***	3.75 (2.43) ***	3.56 (2.57) ***	**ns** p=0.07
	✸✸✸	✸✸✸	✸✸✸	✸✸✸	✸✸✸	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Repeated measures ANOVA P<0.001✸✸✸ Paired sample t-test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : One-way ANOVA (not significant)

7.2 SECONDARY OUTCOME MEASURES

7.2.1 SELF REPORT VERBAL RATING SCALES

7.2.0 Secondary outcome measures

7.2.1 Self report verbal rating scales

Study participant response, to a series of verbal enquiries, were recorded by the clinician at four weekly intervals.

7.2.1.1 Present pain intensity (PPI)

PPI measured the presence of TMJ pain or discomfort : None / Mild / Moderate/ Severe.

Detailed results are recorded in tables (22) and graphically illustrated in figure (33).

Analysing all groups together, a significant reduction in PPI ($p<0.001$) was recorded at all time points; four, eight and twelve weeks; in both the pragmatic and imputation analyses.

TMJ discomfort and pain was reported by the patient to be non existent or mild in 104/250 (65%) completers analysis and 154/250 (62%) in the more conservative imputation analysis.

Intra group imputation analysis revealed a significant reduction in PPI at the end of treatment ($p<0.001$) in groups 1,3 and 4, ($p<0.005$) in group 2.

On treatment completion, nonexistent or mild TMJ discomfort was recorded as 42/63 (67%) group 1 (SSRI), 33/63 (52%) group 2 (placebo), 44/62 (71%) group 3 (splint) and 35/62 (57%) group 4 (splint and SSRI).However, intergroup analysis did not reveal a significant difference in superiority for any particular treatment group.

7.2.1.2 Frequency scores

Frequency was classified as : Never / Occasionally / Often / Always.

Detailed results are recorded in tables 23 and illustrated in figure 34.

All groups, both together and individually revealed significant improvement in scores at each time point; 4,8 and 12 weeks ($p<0.001$).

On treatment completion, participants reported never or occasional TMJ pain or discomfort in: 48% (72/151) in the pragmatic analysis and 35% (87/250) in the imputation analysis.

There was no significant difference in reported improvement between groups.

7.2.1.3 Pain response

This was recorded as Worse / In pain / Improved / Pain free

Detailed results are shown in tables 24 and illustrated graphically in figure 35.

Amongst all groups there is a significant improvement in pain response rating ($p<0.001$).

Study participants reported pain improvement or complete resolution of pain in 65% (104/161). Intra group analysis revealed this to be highest in the splint only group 74% (28/38) and fluoxetine only groups 68% (25/37).

However, intergroup analysis did not substantiate any significant difference in improvement between scores.

7.2.1.4 Interference with life

The tables of dichotomous Yes / No results are shown in tables 25, figure 36.

There was a highly significant decrease in pain interference in everyday life in all individual groups during the course of treatment in both the pragmatic and imputation analyses. This was significant at all time points 4,8 and 12 weeks ($p<0.001$). On treatment completion no interference with life was recorded as 72% (114/159) pragmatic analysis but slightly lower 53% (130/250) in the imputation analysis although still a highly significant reduction ($p<0.001$). There was no intergroup variation in the successful outcome between groups.

Table 22 a: Secondary outcome measures – Present pain intensity PPI (Completers analysis) during the study

Week	PPI	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
0	None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	ns p=0.490
	Mild	106 (42.4%)	25 (39.7%)	26 (41.3%)	30 (48.4%)	25 (40.3%)	
	Moderate	97 (38.8%)	22 (34.9%)	29 (46.0%)	23 (37.1%)	23 (37.1%)	
	Severe	47 (18.8%) n=250	16 (25.4%)n=63	8 (12.7%) n=63	9 (14.5%) n=62	14 (22.6%) n=62	
4	None	16 (8.4%) ***	3 (6.7%) *	4 (8.2%)	6 (12.8%) **	2 (4.2%) *	ns p=0.558
	Mild	93 (48.7%)	24 (51.1%)	23 (46.9%)	23 (48.9%)	23 (47.9%)	
	Moderate	62 (32.5%)	10 (21.3%)	18 (36.7%)	16 (34.0%)	18 (37.5%)	
	Severe	20 (10.5%) n=191	9 (19.1%) n=47	4 (8.2%) n=49	2 (4.3%) n=47	5 (10.4%) n=48	
8	None	22 (12.4%) ***	5 (11.6%) **	7 (14.9%) **	5 (11.6%) *	5 (11.1%) **	ns p=0.687
	Mild	89 (50.0%)	18 (41.9%)	23 (48.9%)	21 (48.8%)	27 (60.0%)	
	Moderate	52 (29.2%)	15 (34.9%)	13 (27.7%)	16 (37.2%)	8 (17.8%)	
	Severe	15 (8.4%) n=178	5 (11.6%) n=43	4 (8.5%) n=47	1 (2.3%) n=43	5 (11.1%) n=45	
12	None	30 (18.2%) ***	5 (13.2%) **	9 (21.4%) ***	9 (22.5%) **	7 (15.6%) *	ns p=0.305
	Mild	77 (46.7%)	19 (50.0%)	18 (42.9%)	21 (52.5%)	19 (42.2%)	
	Moderate	45 (27.3%)	11 (28.9%)	13 (31.0%)	7 (17.5%)	14 (31.1%)	
	Severe	13 (7.9%) n=165	3 (7.9%) n=38	2 (4.8%) n=42	3 (7.5%) n=40	5 (11.1%) n=45	
		***	***	**	**	***	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Inter group anaysis : Kruskall -Wallis (not significant)
Intra group analysis : Friedman significance P<0.0001*** Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***

Table 22 b: Secondary outcome measures – Present pain intensity PPI scores (Imputation analysis) during the study.

Week	PPI	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
0	None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	ns p=0.490
	Mild	106 (42.4%)	25 (39.7%)	25 (39.7%)	30 (48.4%)	26 (41.9%)	
	Moderate	97 (38.8%)	23 (36.5%)	29 (46.0%)	22 (35.5%)	23 (37.1%)	
	Severe	47 (18.8%)	15 (23.8%)	9 (14.3%)	10 (16.1%)	13 (21%)	
4	None	16 (6.4%)	3 (4.8%)	5 (7.9%)	7 (11.3%)	1 (1.6%)	ns p=0.431
	Mild	122 (48.8%)	32 (50.8%)	26 (41.3%)	33 (53.2%)	31 (50%)	
	Moderate	80 (32%) ***	14 (22.2%) *	27 (42.9%) *	15 (24.2%) **	24 (38.7%) *	
	Severe	32 (12.8%)	14 (22.2%)	5 (7.9%)	7 (11.3%)	6 (9.7%)	
8	None	22 (8.8%)	4 (6.3%)	8 (12.7%)	6 (9.7%)	4 (6.5%)	ns p=0.793
	Mild	127 (50.8%)	31 (49.2%)	27 (42.9%)	33 (53.2%)	36 (58.1%)	
	Moderate	74 (29.6%) ***	18 (28.6%) **	23 (36.5%) **	17 (27.4%) *	16 (25.8%) **	
	Severe	27 (10.8%)	10 (15.9%)	5 (7.9%)	6 (9.7%)	6 (9.7%)	
12	None	30 (12%)	5 (7.9%)	9 (14.3%)	9 (14.5%)	7 (11.3%)	ns p=0.384
	Mild	124 (49.6%)	37 (58.7%)	24 (38.1%)	35 (56.5%)	28 (45.2%)	
	Moderate	70 (28%) ***	13 (20.6%) ***	26 (41.3%) **	10 (16.1%) ***	21 (33.9%) **	
	Severe	26 (10.4%)	8 (12.7%)	4 (6.3%)	8 (12.9%)	6 (9.7%)	
		***	***	**	***	***	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001*** Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant)

Figure 33:

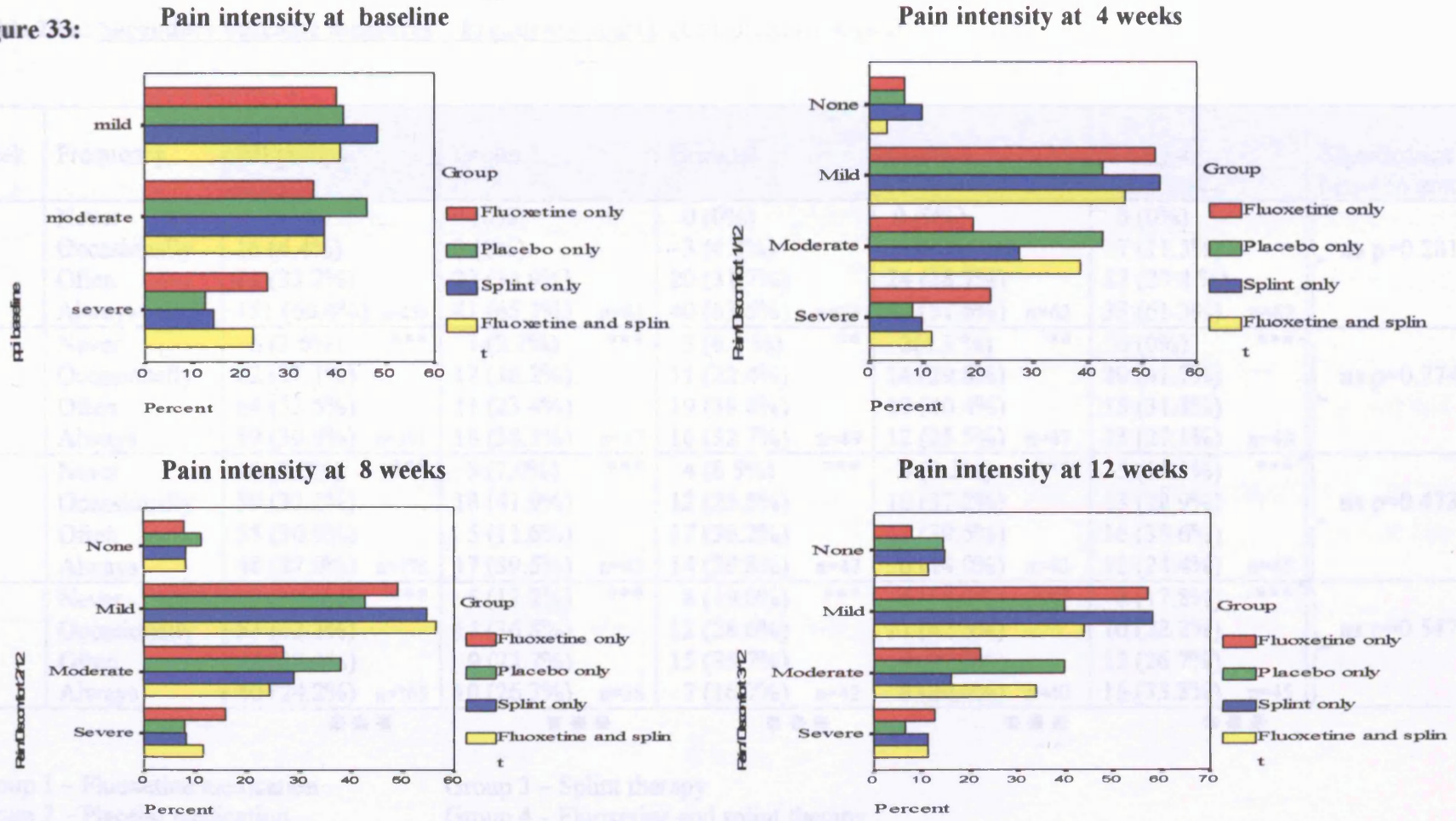

Pain intensity at baseline
mild
moderate
severe
rpi baseline
Group
Fluoxetine only
Placebo only
Splint only
Fluoxetine and splin
t
0 10 20 30 40 50 60
Percent
Pain intensity at 4 weeks
None
Mild
Moderate
Severe
RainDiscomfort 1V12
Group
Fluoxetine only
Placebo only
Splint only
Fluoxetine and splin
t
0 10 20 30 40 50 60
Percent
Pain intensity at 8 weeks
None
Mild
Moderate
Severe
RainDiscomfort2V12
Group
Fluoxetine only
Placebo only
Splint only
Fluoxetine and splin
t
0 10 20 30 40 50 60
Percent
Pain intensity at 12 weeks
None
Mild
Moderate
Severe
RainDiscomfort3V12
Group
Fluoxetine only
Placebo only
Splint only
Fluoxetine and splin
t
0 10 20 30 40 50 60 70
Percent

Table 23 a: Secondary outcome measures – Frequency scores (Completers analysis)

Week	Frequency	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
0	Never	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	ns p=0.281
	Occasionally	16 (6.4%)	0 (0%)	3 (4.8%)	6 (9.7%)	7 (11.3%)	
	Often	83 (33.2%)	22 (34.9%)	20 (31.7%)	24 (38.7%)	17 (27.4 %)	
	Always	151 (60.4%) n=250	41 (65.1%) n=63	40 (63.5%) n=63	32 (51.6%) n=62	38 (61.3%) n=62	
4	Never	6 (3.6%) ***	1 (2.1%) ***	3 (6.1 %) **	2(4.3 %) **	0 (0%) ***	ns p=0.774
	Occasionally	62 (37.1%)	17 (36.2%)	11 (22.4%)	14 (29.8%)	20 (41.7%)	
	Often	64 (33.5%)	11 (23.4%)	19 (38.8%)	19 (40.4%)	15 (31.3%)	
	Always	59 (30.9%) n=191	18 (38.3%) n=47	16 (32.7%) n=49	12 (25.5%) n=47	13 (27.1%) n=48	
8	Never	16 (9.0%) ***	3 (7.0%) ***	4 (8.5%) ***	4 (9.3%) ***	5 (11.1%) ***	ns p=0.473
	Occasionally	59 (33.1%)	18 (41.9%)	12 (25.5%)	16 (37.2%)	13 (28.9%)	
	Often	55 (30.9%)	5 (11.6%)	17 (36.2%)	17 (39.5%)	16 (35.6%)	
	Always	48 (27.0%) n=178	17 (39.5%) n=43	14 (29.8%) n=47	6 (14.0%) n=43	11 (24.4%) n=45	
12	Never	27 (16.4%) ***	5 (13.2%) ***	8 (19.0%) ***	6 (15.0%) ***	8 (17.8%) ***	ns p=0.547
	Occasionally	53 (32.1%)	14 (36.8%)	12 (28.6%)	17 (42.5%)	10 (22.2%)	
	Often	45 (27.3%)	9 (23.7%)	15 (35.7%)	9 (22.5%)	12 (26.7%)	
	Always	40 (24.2%) n=165	10 (26.3%) n=38	7 (16.7%) n=42	8 (20.0%) n=40	15 (33.3%) n=45	
		***	***	***	***	***	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001*** Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant)

Table 23 b: Secondary outcome measures – Frequency scores (Intention needed to treat analysis)

Week	Frequency	All groups n=250	Group 1 n=63	Group 2 n=63	Group 3 n=62	Group 4 n=62	Significance between groups
0	Never	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	ns p=0.281
	Occasionally	16 (6.4%)	0 (0%)	3 (4.8%)	7 (11.3%)	6(9.7%)	
	Often	83 (33.2%)	23 (36.5%)	21 (33.3%)	22 (35.5%)	17 (27.4 %)	
	Always	151 (60.4%)	40 (63.5%)	39 (61.9%)	33 (53.2%)	39 (62.9%)	
4	Never	6 (2.4%) ***	1 (1.6%) ***	3 (4.8 %) **	2(3.2 %) **	0 (0%) ***	ns p=0.565
	Occasionally	66 (26.4%)	19 (30.2%)	12 (19.0%)	14 (22.6%)	21 (33.9%)	
	Often	84 (33.6%)	15 (23.8%)	24 (38.1%)	25 (40.3%)	20 (32.3%)	
	Always	94 (37.6%)	28 (44.4%)	24 (38.1%)	21 (33.9%)	21 (33.9%)	
8	Never	16 (6.4%) ***	3 (4.8%) ***	4 (6.3%) ***	4 (6.5%) ***	5 (8.1%) ***	ns p=0.188
	Occasionally	65 (26.0%)	19 (30.2%)	14 (22.2%)	16 (25.8%)	16 (25.8%)	
	Often	85 (34.0%)	12 (19.0%)	25 (39.7%)	28 (45.2%)	20 (32.3%)	
	Always	84 (33.6%)	29 (46.0%)	20 (31.7%)	14 (22.6%)	21 (33.9%)	
12	Never	27 (10.8%) ***	5 (7.9%) ***	8 (12.7%) ***	6 (9.7%) ***	8 (12.9%) ***	ns p=0.083
	Occasionally	60 (24.0%)	18 (28.6%)	12 (19.0%)	20 (32.3%)	10 (16.1%)	
	Often	77 (30.8%)	16 (25.4%)	24 (38.1%)	20 (32.3%)	17 (27.4%)	
	Always	86 (34.4%)	24 (38.0%)	19 (30.2%)	16 (25.8%)	27 (43.5%)	
		***	***	***	***	***	

Group 1 – Fluoxetine medication Group 3 – Splint therapy
Group 2 – Placebo medication Group 4 – Fluoxetine and splint therapy
Intra group analysis : Friedman significance P<0.0001*** Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant)

Figure 34 :

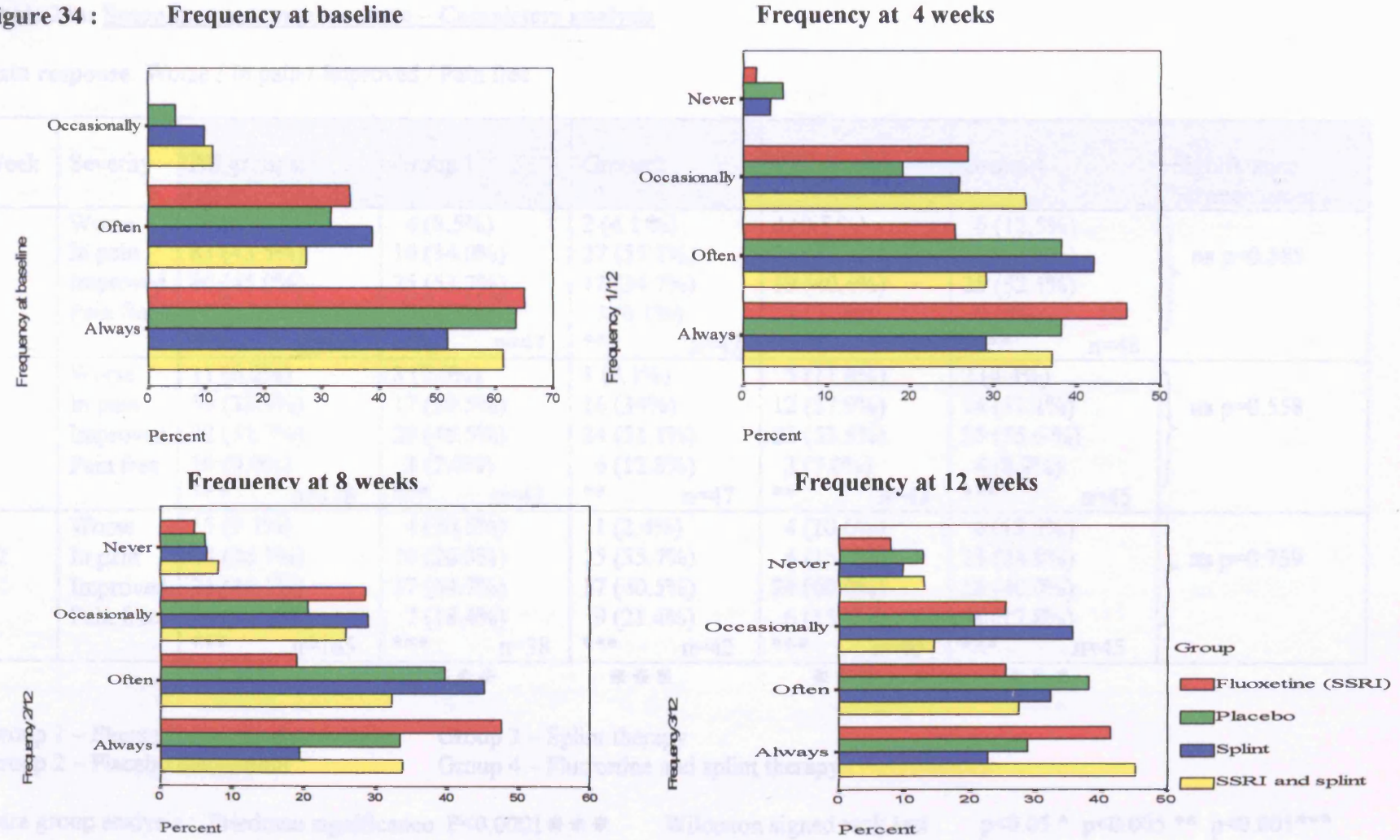

Frequency at baseline
Occasionally
Often
Always
Frequency at baseline
0 10 20 30 40 50 60 70
Percent
Frequency at 4 weeks
Never
Occasionally
Often
Always
Frequency 1/12
0 10 20 30 40 50
Percent
Frequency at 8 weeks
Never
Occasionally
Often
Always
Frequency2/12
0 10 20 30 40 50 60
Percent
Frequency at 12 weeks
Never
Occasionally
Often
Always
Frequency3/12
0 10 20 30 40 50
Percent
Group
Fluoxetine (SSRI)
Placebo
Splint
SSRI and splint

Table 24a: Secondary outcome measure – Completers analysis

Pain response: Worse / In pain / Improved / Pain free

Week	Severity	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
4	Worse	16 (8.4%)	4 (8.5%)	2 (4.1 %)	4 (8.5 %)	6 (12.5%)	**ns** p=0.585
	In pain	83 (43.5%)	16 (34.0%)	27 (55.1%)	23 (48.9%)	17 (35.4%)	
	Improved	86 (45.0%)	25 (53.2%)	17 (34.7%)	19 (40.4%)	25 (52.1%)	
	Pain free	6 (3.1%)	2 (4.3%)	3 (6.1%)	1 (2.1%)	0 (0%)	
		*** n=191	*** n=47	*** n=49	*** n=47	*** n=48	
8	Worse	11 (6.2%)	3 (7.0%)	1 (2.1%)	5 (11.6%)	2 (4.4%)	**ns** p=0.558
	In pain	59 (33.1%)	17 (39.5%)	16 (34%)	12 (27.9%)	14 (31.1%)	
	Improved	92 (51.7%)	20 (46.5%)	24 (51.1%)	23 (53.5%)	25 (55.6 %)	
	Pain free	16 (9.0%)	3 (7.0%)	6 (12.8%)	3 (7.0%)	4 (8.9%)	
		*** n=178	*** n=43	** n=47	** n=43	*** n=45	
12	Worse	15 (9.1%)	4 (10.5%)	1 (2.4%)	4 (10.0%)	6 (13.3%)	**ns** p=0.759
	In pain	44 (26.7%)	10 (26.3%)	15 (35.7%)	6 (15.0%)	13 (28.9%)	
	Improved	76 (46.1%)	17 (44.7%)	17 (40.5%)	24 (60.0%)	18 (40.0%)	
	Pain free	30 (18.2%)	7 (18.4%)	9 (21.4%)	6 (15.0%)	8 (17.8%)	
		*** n=165	*** n=38	*** n=42	*** n=40	*** n=45	
		✸✸✸	✸✸✸	✸✸✸	✸✸✸	✸✸✸	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001✸✸✸ Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant

Table 24b: Secondary outcome measure – Intention needed to treat analysis

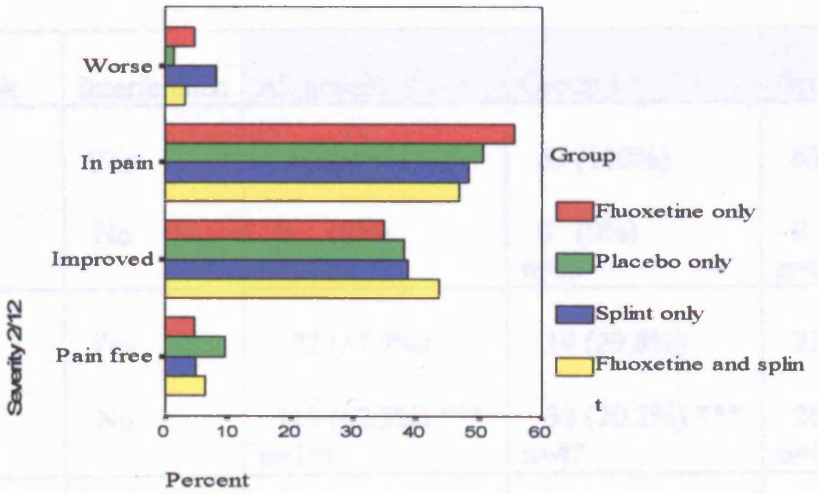
Pain response: Worse / In pain / Improved / Pain free

Week	Severity	All groups n=250	Group 1 n=63	Group 2 n=63	Group 3 n=62	Group 4 n=62	Significance between groups
4	Worse	16 (6.4%)	4 (6.3%)	2 (3.2%)	4 (6.5%)	6 (9.7%)	**ns** p=0.711
	In pain	142 (56.8%)	32 (50.8%)	41 (65.1%)	38 (61.3%)	31 (50.0%)	
	Improved	86 (34.4%) ***	25 (39.7%) ***	17 (27.0%) **	19 (30.6%) **	25 (40.3 %) ***	
	Pain free	6 (2.4%)	2 (3.2%)	3 (4.8%)	1 (1.6%)	0 (0%)	
8	Worse	11 (4.4%)	3 (4.8%)	1 (1.6 %)	5 (8.1 %)	2 (3.2%)	**ns** p=0.502
	In pain	126 (50.4%)	35 (55.6%)	32 (50.8%)	30 (48.4%)	29 (46.8%)	
	Improved	97 (38.8%) ***	22 (34.9%) ***	24 (38.1%) ***	24 (38.7%) ***	27 (43.5%) ***	
	Pain free	16 (6.4%)	3 (4.8%)	6 (9.5%)	3 (4.8%)	4 (6.5%)	
12	Worse	15 (6.0%)	4 (6.3%)	1 (1.6%)	4 (6.5%)	6 (9.7%)	**ns** p=0.950
	In pain	112 (47.6%)	29 (46%)	36 (57.1%)	26 (41.9%)	28 (45.2%)	
	Improved	86 (34.4%) ***	23 (36.5%) ***	17 (27.0%) ***	26 (41.9%) ***	20 (32.3%) ***	
	Pain free	30 (12.0%)	7 (11.1%)	9 (14.3%)	6 (9.7%)	8 (12.9%)	
		***	***	***	***	***	

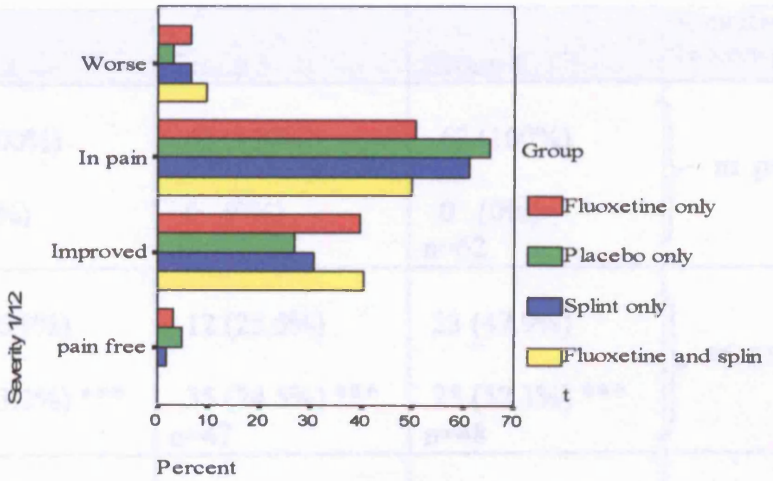
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001*** Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant

Figure 35:
Pain response at 4 weeks



Pain response at 8 weeks



Pain response at 12 weeks

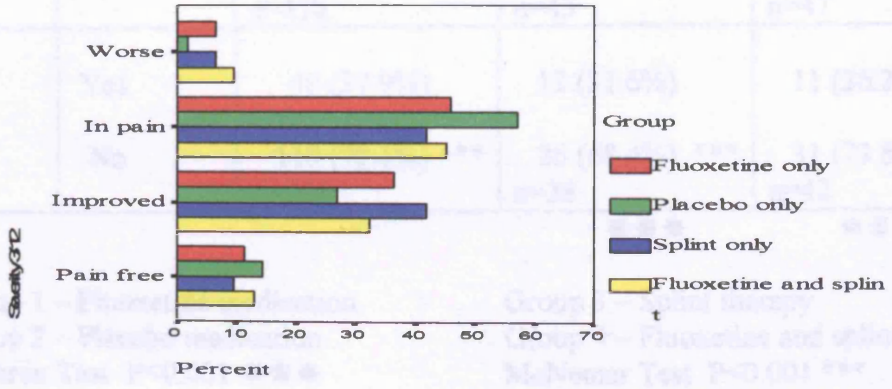


Table 25 a: Secondary outcome measure – Interference with life (Completers analysis)

Week	Interference	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
0	Yes	250 (100%)	63 (100%)	63 (100%)	62 (100%)	62 (100%)	ns p=1.0
	No	0 (0%) n=250	0 (0%) n=63	0 (0%) n=63	0 (0%) n=62	0 (0%) n=62	
4	Yes	72 (37.7%)	14 (29.8%)	23 (46.9%)	12 (25.5%)	23 (47.9%)	ns p=0.043
	No	119 (62.3%) *** n=191	33 (70.2%) *** n=47	26 (53.1%) *** n=49	35 (74.5%) *** n=47	25 (52.1%) *** n=48	
8	Yes	54 (30.3%)	15 (34.9%)	12 (25.5%)	13 (30.2%)	14 (31.1%)	ns p=0.814
	No	124 (69.7%) *** n=178	28 (65.1%) *** n=43	35 (74.5%) *** n=47	30 (69.8%) *** n=43	31 (68.9%) *** n=45	
12	Yes	46 (27.9%)	12 (31.6%)	11 (26.2%)	8 (20.0%)	15 (33.3%)	ns p=0.528
	No	119 (72.1%) *** n=165	26 (68.4%) *** n=38	31 (73.8%) *** n=42	32 (80.0%) *** n=40	30 (66.7%) *** n=45	
			***	***	***	***	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Cochran Test P<0.001 ***

Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
McNemar Test P<0.001 ***

Table 25 b: Secondary outcome measure – Interference with life (Intention to treat analysis)

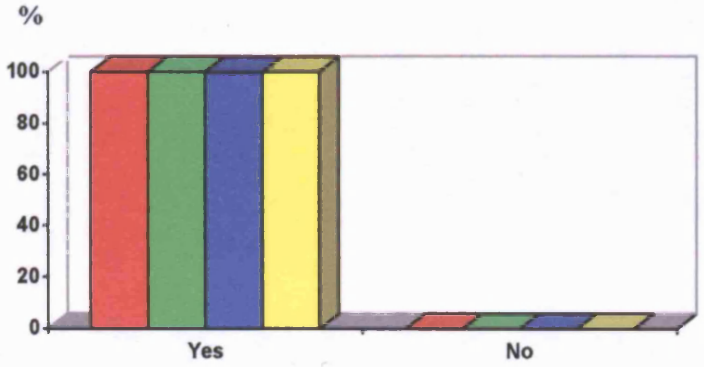
Week	Interference	All groups n=250	Group 1 n=63	Group 2 n=63	Group 3 n=62	Group 4 n=62	Significance between groups
0	Yes	250 (100%)	63 (100%)	63 (100%)	62 (100%)	62 (100%)	ns p=1.0
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
4	Yes	142 (56.8%)	32 (50.8%)	41 (65.0%)	31 (50.0%)	38 (61.3%)	ns p=0.144
	No	108 (43.2%) ***	31 (49.2%) ***	22 (34.9%) ***	31 (50.0%) ***	24 (38.7%) ***	
8	Yes	127 (50.8%)	33 (52.4%)	33 (52.4%)	32 (51.6%)	29 (46.8%)	ns p=0.974
	No	123 (49.2%) ***	30 (47.6%) ***	30 (47.6%) ***	30 (48.4%) ***	33 (53.2%) ***	
12	Yes	120 (48.0%)	28 (44.4%)	32 (50.8%)	31 (50.0%)	29 (46.8%)	ns p=0.965
	No	130 (52.0%) ***	35 (55.6%) ***	31 (49.2%) ***	31 (50.0%) ***	33 (53.2%) ***	
			***	***	***	***	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Cochran Test P<0.001 ***

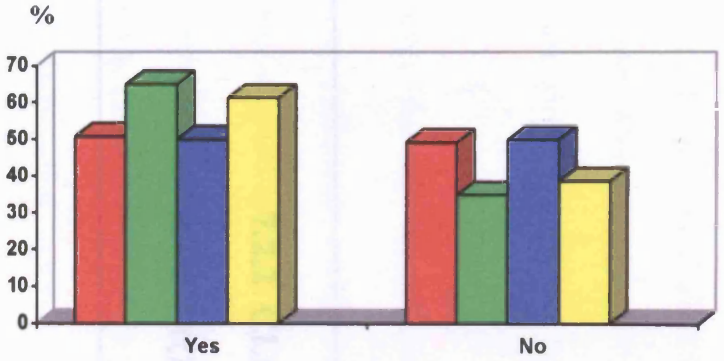
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
McNemar Test P<0.001 ***

Figure 36:

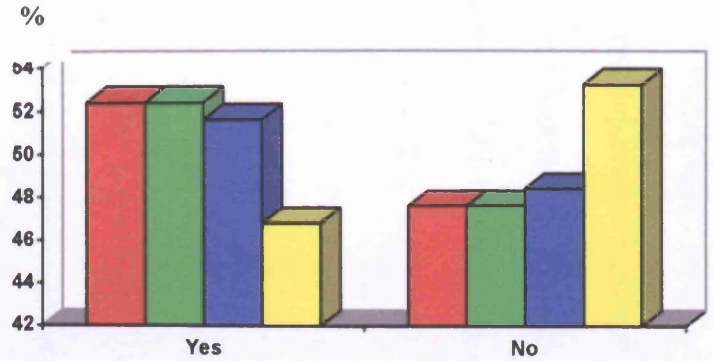
Interference with life at baseline



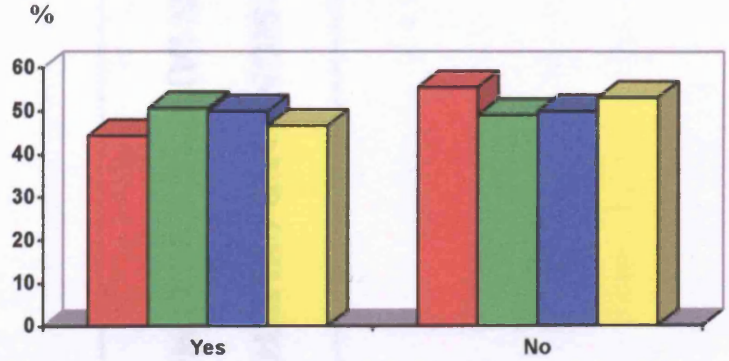
Interference with life at 4 weeks



Interference with life at 8 weeks



Interference with life at 12 weeks



Group 1 (Fluoxetine)
Group 2 (Placebo)
Group 3 (Splint)
Group 4 (Fluoxetine and splint)

7.2.2 CLINICAL SIGNS AND SYMPTOMS AMELIORATION DURING TREATMENT

7.2.2.0 Clinical signs and symptoms

7.2.2.1 Interincisal mouth opening

Parametric statistics were employed for interincisal mouth opening, an interval measure with a true zero and normal distribution curves as illustrated,(figure 37).

7.2.2.1.1 Intra group analysis (Table 26a,b. Figure 38)

Analysing all groups together; the within-subjects general linear model, effects of change in mouth opening, were significant in both the completers and imputation analyses; F(2.3)=6.57,p=0.001 and F(2.4)=3.69 p=0.018 respectively. The multivariate tests revealed significant Wilk's lambda for the completers F(3,162)=3.70, p=0.013, with a significant difference in the measured mouth opening at the 4 time points of a significantly linear (straight line) trend F(1)=11.00,p=0.001.

Analysing all groups together, mouth opening at three months was 2.81mm higher than at baseline for completers (n=165) and 1.38mm higher for imputation analysis (n=250). Paired sample t-tests showed this improvement to be significant in the completers analysis t(164)=3.31,p=0.001 and imputation analysis t(249)=-2.64, p=0.009. The completers analysis also showed significant improvement of 0.18mm between baseline and two months t(177)=2.48,p=0.014.

Individual groups showed an overall trend towards increased mouth opening over the twelve weeks study period. Within subject effects of mouth opening in placebo were significant in both the completers and imputation analyses. F (2.5)=4.65,p=0.007 and F(3) =3.79, p=0.017 respectively. Wilk's lambda F(3,39)=3.9,p=0.016 and F(3,60)=3.42,p=0.023, were consistent with the significant linear trend F(1)=9.71, p=0.003 and F(1)=8.29,p=0.005. In the splint only, group 3, measurements were just

significant in the completers analysis F(1)=, p=0.028 but not the imputation analysis (p=0.182).

Group 1 (SSRI) and Group 4 (SSRI and splint) did not reach a significant level of improvement over the 12 weeks p=0.167 and p=0.701 respectively.

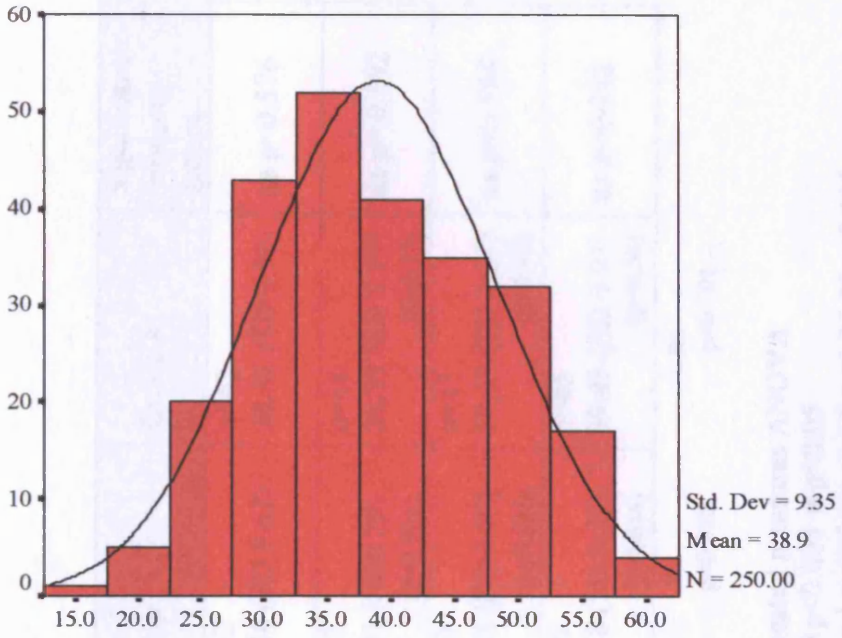
Examining individual groups using the completers analysis mouth opening improves in both the splint and placebo groups. In group 3 (splint) mouth opening from baseline is 1.95mm significantly higher at one month t(46)=2.22,p=0.031, 1.95mm significantly higher at two months F(42)=2.30,p=0.026 and 2.02mm significantly higher at three months F(39)=2.08,p=0.044. Group 2 (placebo) shows a significant improvement from baseline to two months of 2.52mm, t(46),2.71,p=0.009 and to three months of 3.99mm, t(41)=2.71,p=0.010.In group 2 (placebo) mouth opening from baseline is1.28mm significantly higher at two months t(62)=-2.55,p=0.013 and 1.77mm significantly higher at three months t(62) =-2.44,p=0.017. From one month it is 1.47mm significantly higher at three months t(62) -2.35,p=0.022.Unusually, therefore it would appear those patients receiving placebo medication improved most significantly.

7.2.2.1.2. **Inter group analysis** (Table 26a,b)

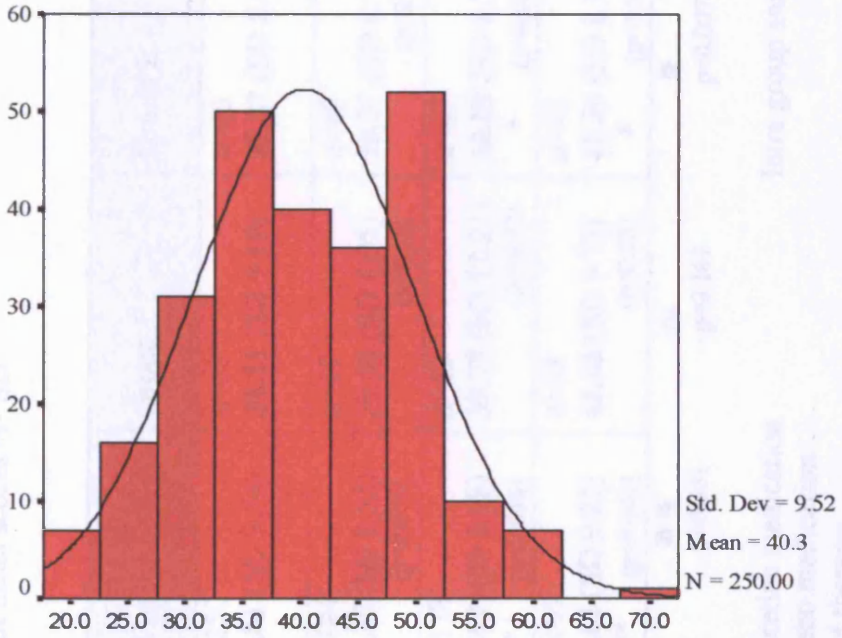
Although it appeared that mouth opening improved most significantly amongst those on placebo medication, intergroup analysis showed that there was no difference between improvement amongst the four groups.

The one-way ANOVA, for intergroup analysis, was non significant between groups at all time points.

Figure 37: Interincisal mouth opening



TMJ interincisal opening, baseline



TMJ interincisal opening 3/12

Table 26 a: **Secondary outcome measures - Interincisal mouth opening (measured in mm) Completers analysis**

A comparison of mean scores +/- SD

Week	All groups	Group 1	Group 2	Group 3	Group 4	Significance between groups
0	n=250 **38.81** (SD 9.36)	n=63 **38.21** (SD 9.19)	n=63 **38.37** (SD 8.69)	n=62 **40.26** (SD 9.62)	n=62 **38.42** (SD 9.99)	**ns** p=0.576
4	n=184 **39.88** (SD 8.52) (p=0.056)	n=47 **39.06** (SD 8.05) (p=0.81)	n=49 **39.37** (SD 8.18) (p=0.28)	n=47 **42.21** (SD8.56) * (p=0.031)	n=48 **38.92** (SD 9.09) (p=0.45)	**ns** p= 0.192
8	n=178 **40.62** (SD 9.78) * (p=0.014)	n=43 **39.79** (SD 12.21) (p=0.92)	n=47 **40.89** (SD 8.75) * (p=0.009)	n=43 **42.21** (SD 8.59) * (p=0.026)	n=45 **39.62** (SD 9.21) (p=0.41)	**ns** p=0.534
12	n=165 **41.62** (SD 9.22) ** (p=0.001)	n=38 **42.66** (SD 9.73) (p=0.08)	n=42 **42.36** (SD 8.71) * (p=0.010)	n=40 **42.28** (SD 8.32) * (p=0.044)	n=45 **39.49** (SD 9.93) (p=0.56)	**ns** p=0.342
	✸✸ p=0.001	ns p=0.167	✸ p=0.007	✸ p=0.028	ns p=0.701	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis: Repeated measures ANOVA
✸✸p<0.005 ✸p<0.05
Paired samples t-test * p<0.05 **p<0.005

Intergroup analysis: One-way ANOVA - not significant

Table 26 b: Secondary outcome measures - Interincisal mouth opening (measured in mm) Imputaion analysis

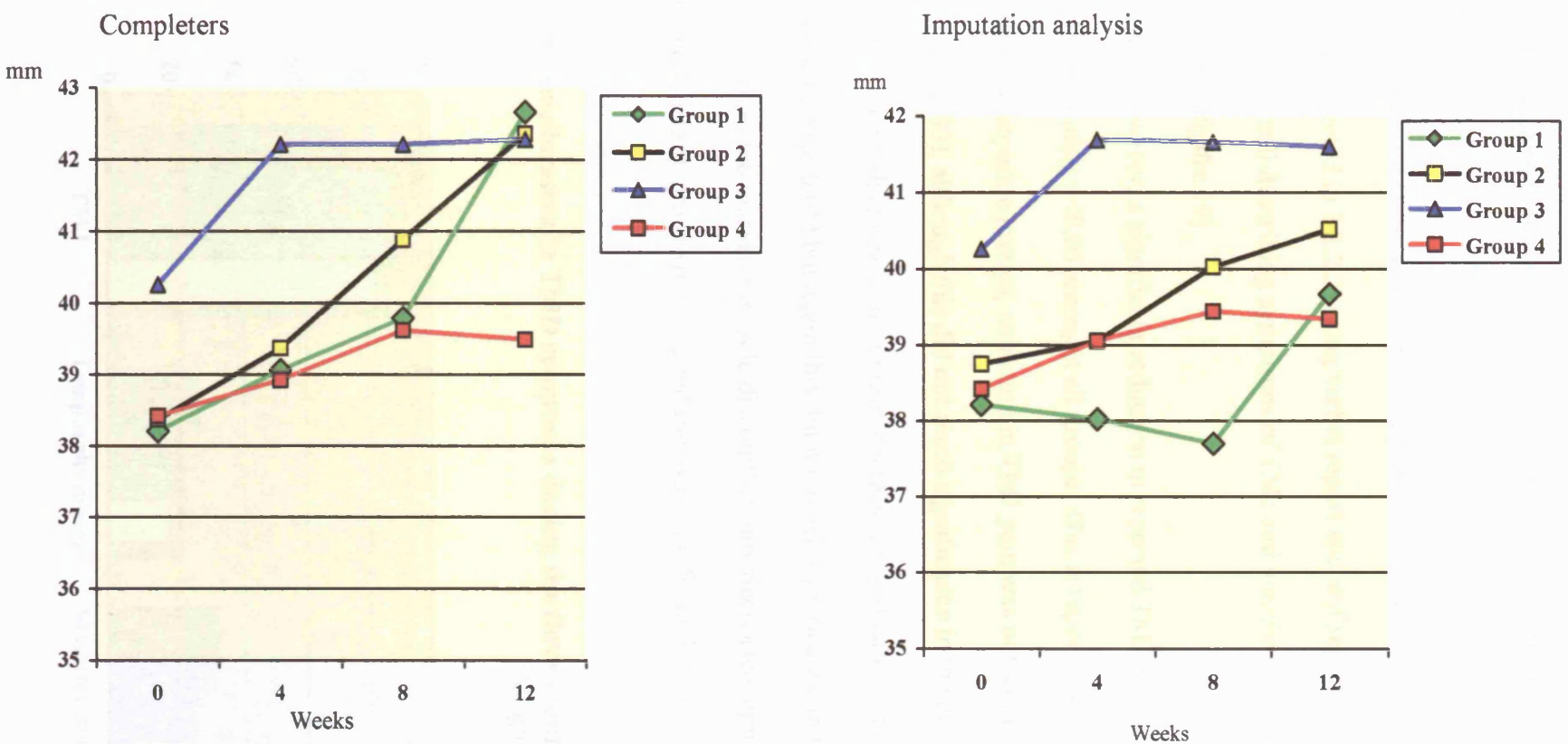
A comparison of mean scores +/- SD

Week	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance between groups
0	38.90 (SD 9.35)	38.21 (SD 9.19)	38.75 (SD 8.67)	40.26 (SD 9.62)	38.42 (SD 9.99)	**ns** p=0.610
4	39.44 (SD 8.94) (p=0.135)	38.02 (SD 8.64) (p=0.809)	39.05 (SD 8.68) (p=0.545)	41.69 (SD 8.43) (p=0.059)	39.05 (SD 9.76) (p=0.445)	**ns** p=0.123
8	39.70 (SD 9.78) (p=0.101)	37.70 (SD 11.42) (p=0.699)	40.03 (SD 9.08) * (p=0.013)	41.66 (SD 8.51) (p=0.089)	39.44 (SD 9.68) (p=0.340)	**ns** p=0.155
12	40.28 (SD 9.52) * (p=0.009)	39.67 (SD 10.18) (p=0.188)	40.52 (SD 9.45) * (p=0.017)	41.60 (SD 8.18) (p=0.173)	39.34 (SD 10.17) (p=0.488)	**ns** p=0.555
	✸ p=0.018	ns p=0.219	✸ p=0.017	ns p=0.182	ns p=0.708	

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis: GLM repeated measures ANOVA
✸✸p<0.005 ✸p<0.05
Paired samples t-test * p<0.05 **p<0.005
Intergroup analysis: One-way ANOVA - not significant

Figure 38: **Interincisal mouth opening A comparison of mean scores**



Group 1 – Fluoxetine medication
Group 2 – placebo medication
Group 3 – Splint therapy
Group 4 – Splint and fluoxetine.

7.2.2.2 TMJ signs and symptoms

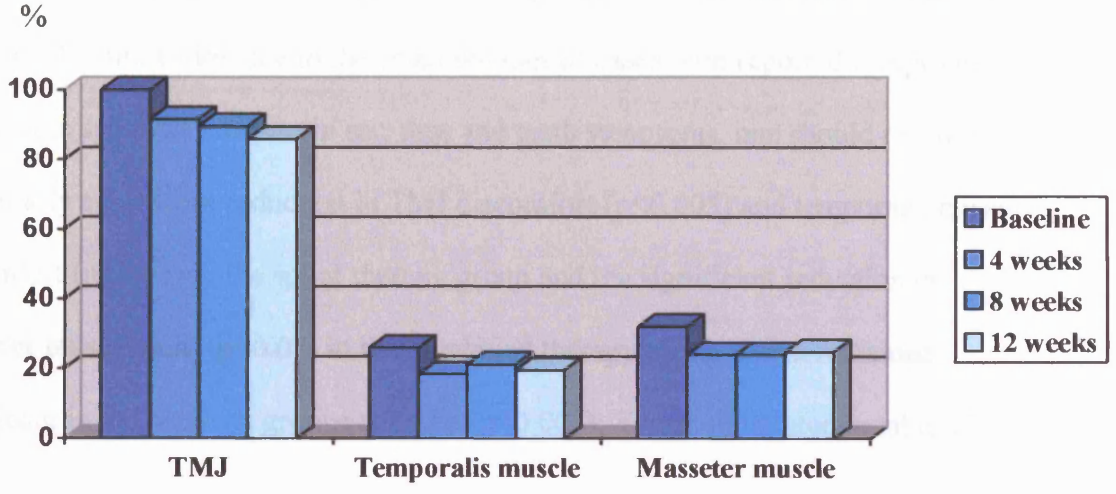
During the treatment phase symptoms and signs were recorded at four weekly intervals.

Despite significant reduction in recorded pain severity, intensity and interference scores, as reported in 7.2.2.3, using verbal report and self report pain questionnaires, patients were still describing symptoms of TMJ and muscle pain throughout the course of the study,(figure 39)

There was however, a significant reduction in reported TMJ pain $p<0.001$ and in muscle discomfort $p<0.05$ amongst all groups. This is reported in detail in table 27.

Analysed in separate groups, reduction in TMJ pain was not significant in the SSRI group ($p=0.080$), although this did not reach significance in the between groups analysis. Temporalis muscle discomfort decreased significantly only in the splint therapy group ($p<0.05$) but again this did not reach significance in the between groups analysis. Reported masseter muscle discomfort only decreased significantly in the combined therapy group ($p<0.05$) and this was significant between groups ($p=0.008$).

Fig. 39: Amelioration in TMD symptoms during the three month treatment phase
(All groups n=250)



7.2.2.3 Character of TMJ pain

The character of pain notably dull and sharp decreased significantly in all groups ($p<0.001$). Individual group analysis showed a significant reduction in dull pain in the SSRI ($p<0.001$), combined therapy ($p<0.005$) and placebo ($p<0.05$) groups which was significant between groups ($p=0.008$). The detailed account is depicted in table 28 and illustrated in figure 40

7.2.2.4 Chronic recurrent pains

All other reported chronic pains: headache, migraine, neckache, backache and abdominal pain decreased significantly ($p<0.001$) with no overall significant difference between groups. This is illustrated in table 29 and figure 41.

7.2.2.5 Other reported head and neck pains

There appears to be an increase in reported facial pain ($p=0.003$) ear pain ($p=0.005$) and tooth pain ($p=0.009$) in the splint therapy group and this was significant in the between group analysis ($p=0.002$,$p=0.003$ and $p=0.019$ respectively) as illustrated in table 30. One could interpret this as an increased awareness of the face, preauricular region and teeth in those wearing an occlusal appliance. However, results should be interpreted with caution due to the small number of cases with reported symptoms. Despite the apparent increase in ear, face and teeth symptoms, one should recall the particularly significant reduction in TMJ discomfort ($p<0.005$) and temporalis muscle discomfort ($p<0.05$) in the splint therapy group and the significant reduction in masseter muscle pain ($p<0.05$) in the combined therapy group which remained significant in the between groups analysis ($p=0.008$). This is illustrated in table 27.

Table 27: Clinical TMJ symptoms and signs during three month treatment phase (Imputation analysis)

Symptoms	Time	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance (between groups)
TMJ discomfort	Baseline	250 (100%)	63 (100%)	63 (100%)	62 (100%)	62 (100%)	-
	4 weeks	229 (91.6%)	60 (95.2%)	60 (95.2%)	53 (85.5%)	56 (90.3%)	ns p=0.150
	8 weeks	224 (89.6%)	60 (95.2%)	55 (87.3%)	56 (90.3%)	53 (85.5%)	ns p=0.300
	12 weeks	215 (86.0%)	57 (90.5%)	52 (82.5%)	52 (83.9%)	54 (87.1%)	ns p=0.579
		***	ns (p=0.080)	**	**	*	
Muscle discomfort – Temporalis	Baseline	65 (26%)	12 (19%)	17 (27%)	23 (37.1%)	13 (21%)	ns p=0.094
	4 weeks	46 (18.4%)	9 (14.3%)	16 (25.4%)	12 (19.4%)	9 (14.5%)	ns p=0.331
	8 week	53 (21.2%)	12 (19%)	17 (27%)	17 (27.4%)	7 (11.3%)	ns p=0.089
	12 weeks	49 (19.6%)	9 (14.3%)	15 (23.8%)	16 (25.8%)	9 (14.5%)	ns p=0.224
		*	ns (p=0.484)	ns (p=0.827)	*	ns (p=0.191)	
Muscle discomfort – Masseter	Baseline	80 (32%)	14 (22.2%)	25 (39.7%)	20 (32.3%)	21 (33.9%)	ns p=0.205
	4 weeks	60 (24%)	11 (17.5%)	21 (33.3%)	20 (32.3%)	8 (12.9%)	* p=0.012
	8 weeks	60 (24%)	12 (19%)	17 (27.0%)	21 (33.9%)	10 (16.1%)	ns p=0.087
	12 weeks	62 (24.8%)	8 (12.7%)	19 (30.2%)	23 (37.1%)	12 (19.4%)	* p=0.008
		*	ns (p=0.379)	ns (p=0.112)	ns (p=0.849)	*	
Signs							
Right TMJ tender to palpate	Baseline	162 (64.8%)	39 (61.9%)	41 (65.1%)	39 (62.9%)	43 (69.4%)	ns p=0.827
	4 weeks	122 (48.8%)	28 (44.4%)	30 (47.6%)	31 (50.0%)	33 (53.2%)	ns p=0.793
	8 weeks	128 (51.2%)	24 (38.1%)	38 (60.3%)	33 (53.2%)	33 (53.2%)	ns p=0.085
	12 weeks	133 (53.2%)	29 (46.0%)	39 (61.9%)	32 (51.6%)	33 (53.2%)	ns p=0.350
		***	**	ns (p=0.051)	ns (p=0.164)	*	
Left TMJ tender to palpate	Baseline	173 (69.2%)	41 (65.1%)	43 (68.3%)	46 (74.2%)	43 (69.4%)	ns p=0.740
	4 weeks	162 (64.8%)	42 (66.7%)	42 (66.7%)	41 (66.1%)	37 (59.7%)	ns p=0.812
	8 weeks	153 (61.2%)	46 (73.0%)	33 (52.4%)	38 (61.3%)	36 (58.1%)	ns p=0.110
	12 weeks	148 (59.2%)	41 (65.1%)	32 (50.8%)	39 (62.9%)	36 (58.1%)	ns p=0.372
		*	ns (p=0.499)	*	ns (p=0.143)	ns (p=0.303)	

Muscle discomfort only decreased significantly between groups in the combined therapy group.

Table 28: Character of pain reported during three month treatment phase (Imputation analysis)

Character	Time	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance (between groups)
Dull ache	Baseline	161 (64.4%)	43 (68.3%)	33 (52.4%)	45 (72.6%)	40 (64.5%)	ns (p=0.103)
	4 weeks	134 (53.6%)**	29 (46.0%)*	34 (54.0%)	39 (62.9%)	32 (51.6%)	ns (p=0.294)
	8 weeks	121 (48.4%)***	28 (44.4%)**	27 (42.9%)	40 (64.5%)*	26 (41.9%)	* p=0.034
	12weeks	111 (44.4%)***	23 (36.5%)***	23 (36.5%)	39 (62.9%)**	26 (41.9%)	* p=0.008
		***	***	*	ns (p=0.382)	**	
Discomfort	Baseline	137 (54.8%)	35 (55.6%)	37 (58.7%)	33 (53.2%)	32 (51.6%)	ns (p=0.868)
	4 weeks	152 (60.8%)	40 (63.5%)	36 (57.1%)	39 (62.9%)	37 (59.7%)	ns (p=0.875)
	8 weeks	154 (61.6%)	34 (54.0%)	38 (60.3%)	43 (69.4%)	39 (62.9%)	ns (p=0.360)
	12weeks	140 (56.0%)	33 (52.4%)	35 (55.6%)	36 (58.1%)	36 (58.1%)	ns (p=0.907)
		ns (p=0.089)					
Sharp	Baseline	99 (39.6%)	27 (42.9%)	30 (47.6%)	17 (27.4%)	25 (40.3%)	ns (p=0.120)
	4 weeks	67 (26.8%)***	16 (25.4%)*	19 (30.2%)*	14 (22.6%)	18 (29.0%)	ns (p=0.766)
	8 weeks	62 (24.8%)***	18 (28.6%)	16 (25.4%)*	15 (24.2%)	13 (21.0%)**	ns (p=0.803)
	12weeks	64 (25.6%)***	16 (25.4%)*	13 (20.6%)***	16 (25.8%)	19 (30.6%)	ns (p=0.649)
		***	*	***	ns (p=0.774)	*	
Stabbing	Baseline	35 (14.0%)	9 (14.3%)	7 (11.1%)	14 (22.6%)	5 (8.1%)	ns (0.190)
	4 weeks	32 (12.8%)	9 (14.3%)	8 (12.7%)	11 (17.7%)	4 (6.5%)	ns (p=0.293)
	8 weeks	25 (10%)	7 (11.1%)	4 (6.3%)	11 (17.7%)	3 (4.8%)	ns (p=0.072)
	12weeks	31 (12.4%)	4 (6.3%)	8 (12.7%)	10 (16.1%)	9 (14.5%)	ns (p=0.365)
		ns (p=0.258)	ns (p=0.179)	ns (p=0.347)	ns (p=0.417)	ns (p=0.094)	
Throbbing	Baseline	20 (8%)	3 (4.8%)	6 (9.5%)	4 (6.5%)	7 (11.3%)	ns (p=0.530)
	4 weeks	23 (9.2%)	4 (6.3%)	2 (3.2%)	7 (11.3%)	10(16.1%)	ns (p=0.065)
	8 weeks	21 (8.4%)	4 (6.3%)	2 (3.2%)	9 (14.5%)	6(9.7%)	ns (p=0.126)
	12weeks	26 (10.4%)	4 (6.3%)	3 (4.8%)	8 (12.9%)	11(17.7%)	ns (p=0.064)
		ns (p=0.552)	ns (p=0.925)	*	ns (p=0.219)	ns (p=0.094)	
Burning	Baseline	6 (2.4%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.8%)	ns (p=0.553)
	4 weeks	7 (2.8%)	2 (3.2%)	1 (1.6%)	1 (1.6%)	3 (4.8%)	ns (p=0.650)
	8 weeks	4 (1.6%)	1 (1.6%)	1 (1.6%)	2 (4.8%)	0 (0%)	ns (p=0.562)
	12weeks	6 (2.4%)	1 (1.6%)	1 (1.6%)	3 (4.8%)	1 (1.6%)	ns (p=0.553)
		ns (p=0.479)	ns (p=0.392)	ns (p=1.00)	ns (p=0.194)	ns (p=0.101)	

Figure 40: Character of pain described

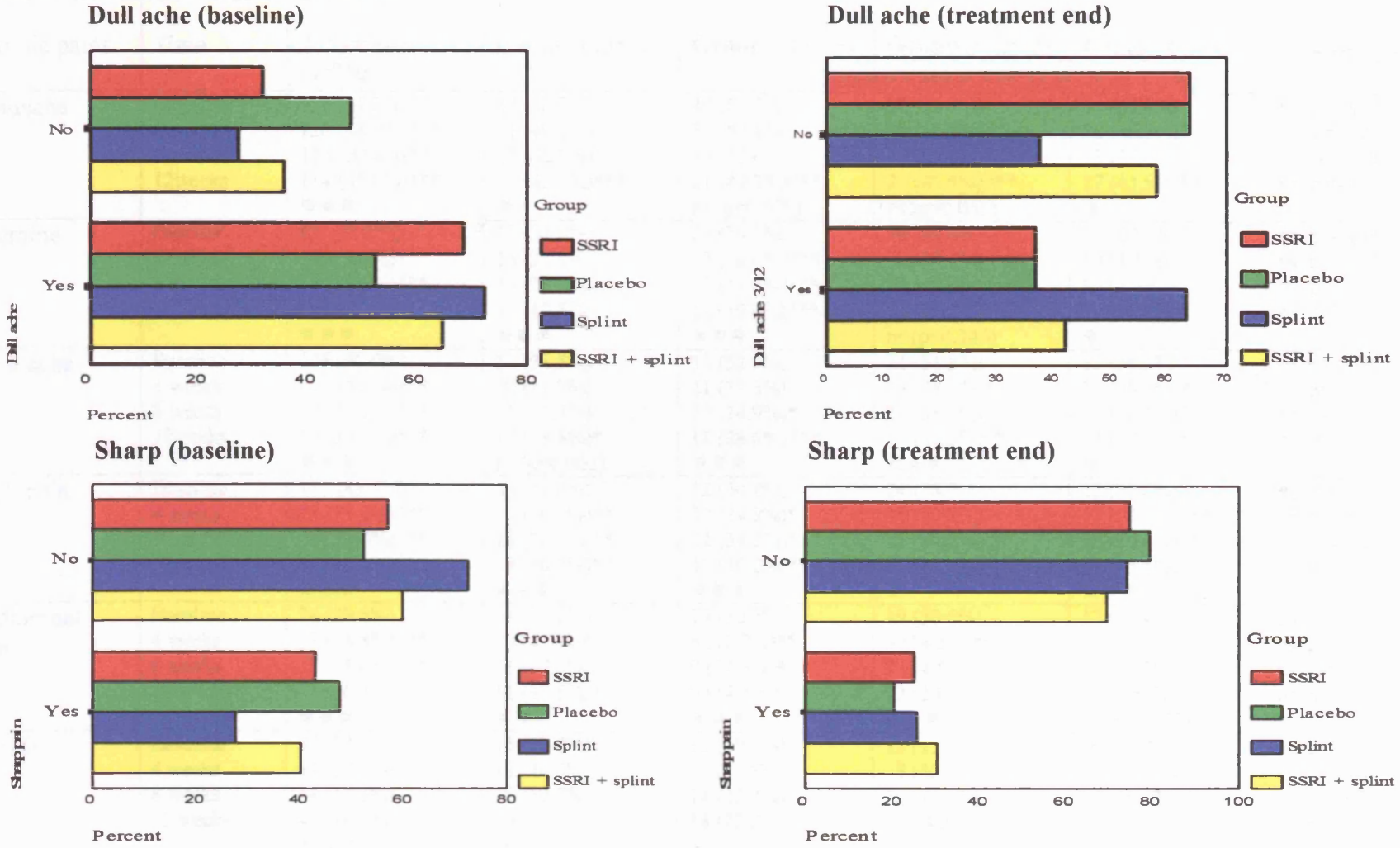
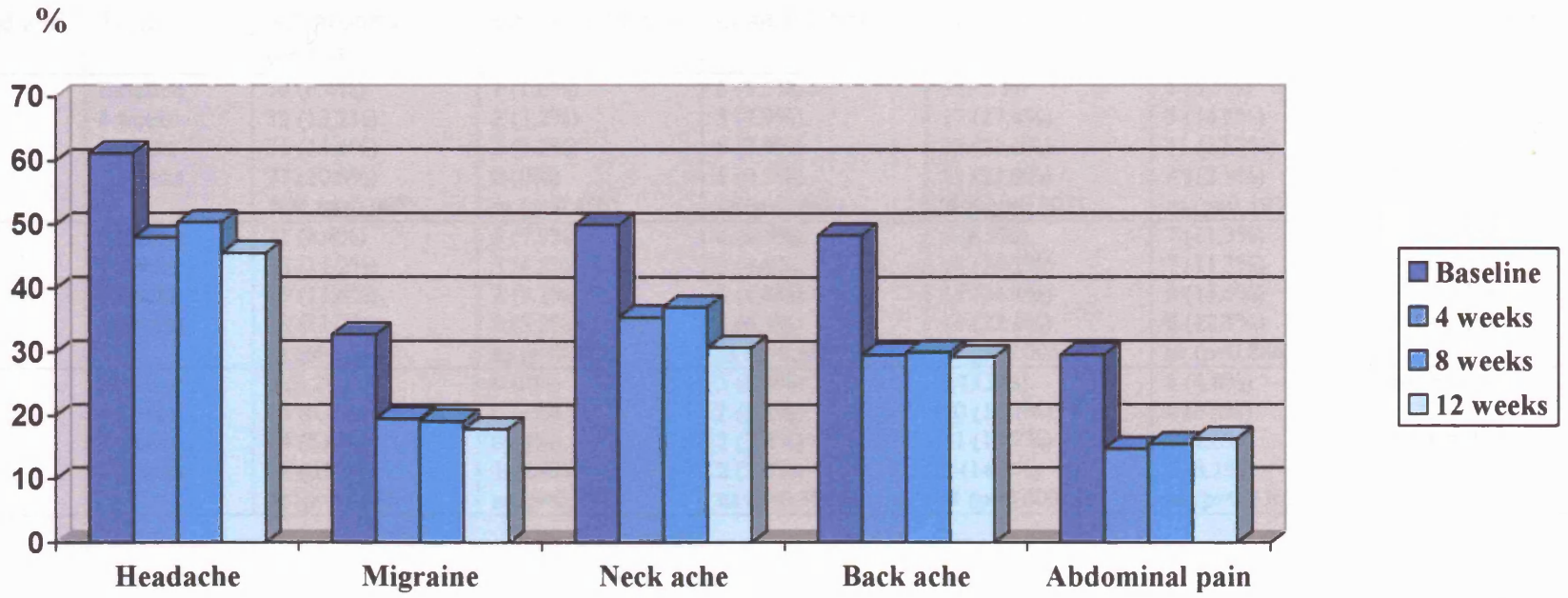


Table 29: Other chronic pains reported during three month treatment phase (Imputation analysis)

Chronic pains	Time	**All groups** (n=250)	**Group 1** (n=63)	**Group 2** (n=63)	**Group 3** (n=62)	**Group 4** (n=62)	Significance between groups
Headache	Baseline	153 (61.2%)	37 (58.7%)	40 (63.5%)	37 (59.7%)	39 (62.9%)	ns p=0.932
	4 weeks	120 (48.0%)***	31 (49.2%)	33 (52 4%)	28 (45.2%)	28 (45.2%)*	ns p=0.820
	8 weeks	126 (50.4%)**	27 (42.9%)*	35 (55.6%)	31 (50.0%)	33 (53.2%)	ns p=0.511
	12weeks	114 (45.6%)***	27 (42.9%)***	31 (49.2%)***	29 (46.8%)***	27 (43.5%)***	ns p=0.882
		***	*	ns (p=0.079)	ns (p=0.055)	*	
Migraine	Baseline	82 (32.8%)	22 (34.9%)	25 (39.7%)	18 (29.0%)	17 (27.4%)	ns p=0.441
	4 weeks	49 (19.6%)***	15 (23.8%)	13 (20.6%)***	12 (19.4%)	9 (14.5%)*	ns p=0.621
	8 weeks	48 (19.2%)***	15 (23.8%)	12 (19.0%)***	12 (19.4%)	9 (14.5%)*	ns p=0.628
	12weeks	45 (18.0%)***	11 (17.5%)*	12 (19.0%)***	12 (19.4%)	10 (16.1%)*	ns p=0.963
		***	***	***	ns (p=0.145)	*	
Neck ache	Baseline	125 (50.0%)	23 (36.5%)	33 (52.4%)	34 (54.8%)	35 (56.5%)	ns p=0.096
	4 weeks	89 (35.6%)***	20 (31.7%)	21 (33.3%)*	24 (38.7%)*	24 (38.7%)**	ns p=0.784
	8 weeks	93 (37.2%)***	21 (33.3%)	22 (34.9%)*	24 (38.7%)*	24 (38.7%)*	ns p=0.753
	12weeks	77 (30.8%)***	15 (23.8%)*	18 (28.6%)***	20 (32.3%)**	24 (38.7%)*	ns p=0.324
		***	ns (p=0.062)	***	***	*	
Back pain	Baseline	121 (48.4%)	33 (52.4%)	32 (50.8%)	24 (38.7%)	32 (51.6%)	ns p=0.372
	4 weeks	74 (29.6%)***	19 (30.2%)**	22 (34.9%)*	16 (25.8%)	17 (27.4%)***	ns p=0.697
	8 weeks	75 (30.0%)***	19 (30.2%)**	22 (34.9%)*	15 (24.2%)	19 (30.6%)**	ns p=0.629
	12weeks	73 (29.2%)***	19 (30.2%)**	19 (30.2%)***	13 (21.0%)*	22 (35.5%)*	ns p=0.351
		***	***	***	*	***	
Abdominal pain	Baseline	74 (29.6%)	19 (30.2%)	19 (30.2%)	19 (30.6%)	17 (27.4%)	ns p=0.979
	4 weeks	37 (14.8%)***	9 (14.3%)*	8 (12.7%)**	9 (14.5%)**	11 (17.7%)	ns p=0.882
	8 weeks	39 (15.6%)***	11 (17.5%)*	9 (14.3%)*	9 (14.5%)*	10 (16.1%)	ns p=0.957
	12 weeks	41 (16.4%)***	11 (17.5%)*	9 (14.3%)*	12 (19.4%)	9 (14.5%)	ns p=0.847
		***	**	***	***	ns (p=0.067)	
Pruritis	Baseline	55 (22%)	15 (23.8%)	12 (19.0%)	12 (19.4%)	16 (25.8%)	ns p=0.749
	4 weeks	44 (17.6%)	13 (20.6%)	15 (23.8%)	8 (12.9%)	8 (12.9%)*	ns p=0.266
	8 weeks	44 (17.6%)	8 (12.7%)	14 (22.2%)	10 (16.1%)	12 (19.4%)	ns p=0.533
	12 weeks	45 (18.0%)	10 (15.9%)	14 (22.2%)	9 (14.5%)	12 (19.4%)	ns p=0.673
		ns (p=0.153)	ns (p=0.082)	ns (p=0.737)	ns (p=0.576)	*	

Chi squared inter group comparisons for each of the chronic pains was not significant between groups

Figure 41: Amelioration in reported chronic pains during the three month treatment phase (All groups n=250)



There was a significant decrease in all reported chronic pains during the three month treatment phase $p<0.001$ at all three time ponts. However, analysis between groups was not significant.

Table 30: Other reported head and neck pain during the three month treatment phase (Imputation analysis)

Other head and neck pain	Time	**All groups** (n=250)	**Group 1** (n=63)	**Group 2** (n=63)	**Group 3** (n=62)	**Group 4** (n=62)	Significance between groups
Face	Baseline	16 (6.4%)	1 (1.6%)	6 (9.5%)	5 (8.1%)	4 (6.5%)	ns p=0.290
	4 weeks	33 (13.2%)	2 (3.2%)	5 (7.9%)	17 (27.4%)	9 (14.5%)	***p<0.001
	8 weeks	36 (14.4%)	2 (3.2%)	5 (7.9%)	18 (29.0%)	11 (17.7%)	***p<0.001
	12weeks	27 (10.8%)	0 (0%)	6 (9.5%)	13 (21.0%)	8 (12.9%)	** p=0.002
		** (p=0.002)	ns (p=0.468)	ns (p=0.881)	** (p=0.003)	ns (p=0.193)	
Ears	Baseline	21 (8.4%)	5 (7.9%)	4 (6.3%)	5 (8.1%)	7 (11.3%)	ns p=0.791
	4 weeks	28 (11.2%)	3 (4.8%)	3 (4.8%)	15 (24.2%)	7 (11.3%)	**p=0.001
	8 weeks	29 (11.6%)	2 (3.2%)	3 (4.8%)	15 (24.2%)	9 (14.5%)	**p=0.001
	12weeks	28 (11.2%)	2 (3.2%)	4 (6.3%)	14 (22.6%)	8 (12.9%)	* p=0.003
		ns (p=0.338)	ns (p=0.112)	ns (p=0.881)	* (p=0.005)	ns (p=0.886)	
Teeth	Baseline	8 (3.2%)	0 (0%)	3 (4.8%)	2 (3.2%)	3 (4.8%)	ns p=0.344
	4 weeks	16 (6.4%)	0 (0%)	2 (3.2%)	10 (16.1%)	4 (6.5%)	
	8 weeks	14 (5.6%)	0 (0%)	2 (3.2%)	11 (17.7%)	1 (1.6%)	***p<0.001
	12weeks	17 (6.8%)	1 (1.6%)	2 (3.2%)	9 (14.5%)	5 (8.1%)	* p=0.019
		ns (p=0.087)	ns (p=0.392)	ns (p=0.392)	* (p=0.009)	ns (p=0.336)	

7.2.3 PAIN AND PSYCHOSOCIAL SELF-REPORT PAIN QUESTIONNAIRES

Outcome scores at three months

7.2.3.1 Multidimensional pain inventory (MPI)

The patient's perspective of pain; severity, interference, life control and affective distress; had significantly improved during the three months treatment phase amongst the combined groups ($p<0.001$), as illustrated graphically by the box plots (figure 42).The improvement was evident both in the imputation and completers analysis as shown in tables 31a,b.

Analysing all groups, severity ($p<0.001$), interference ($p<0.001$) and affective distress ($p<0.001$) had clearly decreased which consequently resulted in an increase in the patient's perspective of their level of control in life ($p<0.001$).

Intra group analysis suggested severity appeared to reduce most markedly in the splint only and placebo only groups ($p<0.001$), compared to SSRI ($p<0.005$) and combined therapy ($p<0.05$).Improvement in interference was again more marked in the placebo ($p<0.001$) and splint ($p<0.05$) groups with no significant change in SSRI and combined therapy groups. Nevertheless, affective distress was not significantly decreased in the splint only group but was significant in medical therapy groups: SSRI ($p<0.05$), placebo ($p<0.005$) and combined therapy ($p<0.05$).Meanwhile, life control only seemed to improve in the SSRI only group ($p<0.005$) with no significant change in the other three groups, in the imputation analysis.

As an incidental finding, level of support by family and friends appeared to decrease in the splint only group ($p<0.05$).

However, all these findings were not substantiated by the inter group analysis which did not reveal any significant difference in change in scores between the four treatment groups.

7.2.3.2 McGill pain questionnaire (MPQ)

Analysing groups together, all scores significantly improved during the three month treatment phase both in the imputation and completers analysis VAS ($p<0.001$), PPI ($p<0.001$), total % ($p<0.001$), sensory % ($p<0.001$) and affective % ($p<0.001$). Detailed results are reported in table 27a,b and illustrated in figure 31. Intra group analysis suggests VAS pain severity significantly decreased only in the placebo and splint only groups ($p<0.005$).However, inter group analysis revealed no significant difference in improvement in all scores between groups.

7.2.3.3 Beck Depression index (BDI)

Analysing combined groups, there appeared to be a significant reduction in composite score ($p<0.005$).However, this indicates a reduction from a median score of 7.00 to 6.00 which indicates the majority of patients were not depressed, either at baseline or follow up. Despite this minimal reduction in score in each group, intra group analysis suggests only placebo ($p<0.05$) and splint ($p<0.05$) show a significant reduction in score. However, this finding was not substantiated by intergroup analysis which as expected showed a non significant difference in score reduction between the 4 groups.

7.2.3.4 Kellner illness attitude

Kellner disease phobia did not significantly decrease during the course of treatment. Hypochondriacal beliefs and illness attitude reduced in the completers analysis of all groups ($p<0.05$).Intra group analysis suggests the SSRI group in both completers and imputation analysis had a significant reduction in hypochondriacal beliefs ($p<0.05$) but this was not confirmed as significant in the between groups analysis.

Results are shown in tables 32a,b and illustrated by box plots in figures 43.

Table 31 a:

Multidimensional pain inventory (MPI) A comparison of median scores (25^{th},75^{th} percentiles) between the start and finish of the three months. (Completers analysis)

MPI	Study	All groups	Group 1	Group 2	Group 3	Group 4	significance
Patients perspective of pain							
MPI - Severity	Start	3.00 (1.92,4.00)	3.33 (2.00,4.33)	3.00 (2.33,4.00)	2.66 (1.33,3.40)	2.66 (1.65,4.00)	ns p=0.105
	Finish	2.00 (1.00,3.33) ***	2.33 (1.11,3.50) **	2.00 (1.00,3.66) ***	2.00 (0.60,2.92) ***	2.00 (1.32,3.63) *	ns p=0.380
MPI - Interference	Start	1.45 (0.65,2.88)	1.90 (0.82,3.36)	1.63 (0.80,2.90)	1.36 (0.45,2.27)	1.24 (0.52,2.65)	ns p=0.103
	Finish	0.90 (0.30,2.36) ***	0.86 (0.20,2.36) ***	1.00 (0.45,2.18) ***	0.65 (0.18,2.46) *	0.90 (0.41,2.55)	ns p=0.808
MPI – Life control	Start	3.25 (2.31,4.00)	3.25 (2.00,4.00)	3.25 (2.25,4.25)	3.25 (2.46,4.00)	3.38 (2.50,4.25)	ns p=0.780
	Finish	3.75 (2.75,4.25) ***	3.75 (3.00,4.50) **	3.75 (3.25,4.50) *	3.50 (2.75,4.25) *	3.25 (2.50,4.25)	ns p=0.544
MPI – Affective distress	Start	3.33 (2.33,4.30)	3.33 (2.33,4.30)	3.60 (2.65,4.40)	3.00 (2.00,4.00)	3.32 (2.32,4.30)	ns p=0.235
	Finish	3.00 (1.66,3.66) ***	3.00 (1.53,4.00) *	3.00 (1.50,3.47) **	3.00 (1.66,3.92)	3.00 (2.00,4.00) *	ns p=0.960
Response of significant other							
MPI – Support response	Start	3.33 (2.30,4.66)	3.60 (2.25,4.66)	3.66 (2.32,5.00)	3.00 (2.33,4.33)	3.00 (2.00,4.33)	ns p=0.681
	Finish	3.60 (2.33,4.33)	3.60 (2.66,4.32)	3.15 (2.33,4.66)	3.66 (2.60,4.00) *	3.60 (2.33,4.53)	ns p=0.961
MPI – Punishing response	Start	1.00 (0,2.06)	0.75 (0.25,2.81)	1.25 (0.25,2.56)	0.75 (0,2.00)	0.75 (0,1.75)	ns p=0.201
	Finish	0.75 (0,1.75)	0.75 (0,1.25)	0.75 (0.06,1.75)	1.00 (0,2.00)	0.75 (0,2.00)	ns p=0.874
MPI – Solicitous response	Start	2.66 (1.50,3.87)	2.83 (1.45,3.63)	2.66 (1.77,4.37)	2.66 (1.50,3.83)	2.50 (1.30,3.83)	ns p=0.929
	Finish	2.83 (1.50,3.83)	2.50 (1.16,4.20)	2.58 (1.41,3.92)	3.16 (2.00,4.16)	2.83 (1.00,3.50)	ns p=0.487
MPI – Distracting response	Start	1.75 (0.75,2.75)	2.00 (0.75,2.75)	1.50 (0.75,3.00)	2.00 (0.75,2.75)	1.75 (0.50,3.00)	ns p=0.959
	Finish	2.00 (0.88,3.00)	2.25 (1.00,3.50)	1.75 (0.75,2.94)	2.00 (0.75,3.00)	2.00 (1.00,3.00)	ns p=0.975
Frequency of participation in							
MPI – Household chores	Start	4.80 (3.60,5.60)	4.80 (3.60,5.60)	4.80 (3.35,5.80)	4.60 (3.40,5.80)	4.80 (3.80,5.40)	ns p=0.961
	Finish	4.40 (3.60,5.20)	4.60 (4.05,5.20)	4.40 (3.00,5.25)	4.40 (3.65,5.24)	4.60 (3.60,5.50)	ns p=0.756
MPI – Outdoor work	Start	2.00 (1.00,3.00)	1.90 (1.28,3.00)	1.90 (0.81,3.15)	2.00 (0.95,3.00)	2.00 (0.80,3.00)	ns p=0.731
	Finish	2.00 (1.00,3.00)	1.68 (1.26,3.15)	2.00 (1.00,2.70)	2.00 (0.75,3.00)	2.33 (1.00,3.31)	ns p=0.736
MPI – Activities away from home	Start	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.75 (2.75,4.50)	3.25 (2.25,4.25)	3.50 (2.50,4.50)	ns p=0.714
	Finish	3.75 (2.75,4.25)	3.75 (3.00,4.25)	3.75 (2.94,4.31)	3.50 (2.75,4.25)	3.25 (2.63,4.50)	ns p=0.707
MPI – Social activities	Start	3.00 (2.30,4.00)	2.75 (2.25,3.75)	3.25 (2.50,4.00)	3.00 (2.33,3.75)	3.38 (2.00,4.06)	ns p=0.655
	Finish	3.25 (2.25,4.00)	3.25 (2.27,4.00)	3.25 (2.44,4.00)	3.13 (2.27,3.62)	3.25 (1.88,3.88)	ns p=0.793
MPI – General activity level	Start	3.38 (2.75,3.91)	3.40 (2.80,3.88)	3.44 (2.68,3.84)	3.31 (2.50,3.79)	3.34 (2.80,4.05)	ns p=0.901
	Finish	3.23 (2.74,3.90)	3.30 (2.68,4.01)	3.20 (2.76,4.01)	3.20 (2.47,3.68)	3.24 (2.89,3.77)	ns p=0.830

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Kruskall Wallice not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p< 0.001$***

Table 31 b:

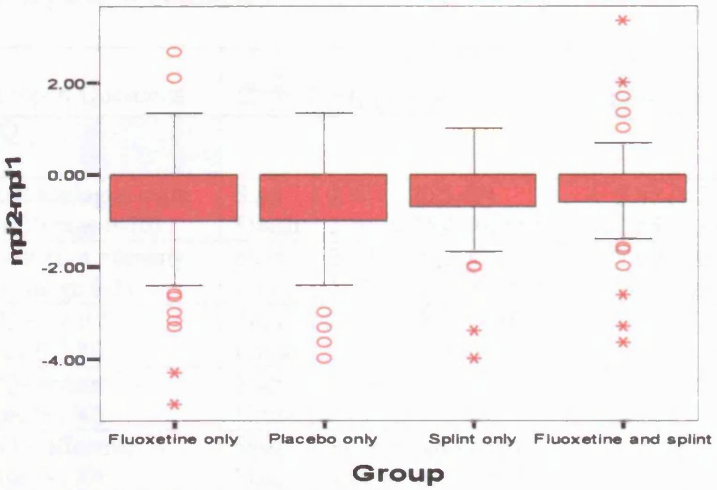
Multidimensional pain inventory (MPI) A comparison of median scores (25^{th},75^{th} percentiles) (Imputation analysis)

MPI	Study	All groups	Group 1	Group 2	Group 3	Group 4	Sig.
Patients perspective of pain							
MPI - Severity	Start	3.00 (1.92,4.00)	3.33 (2.00,4.33)	3.00 (2.33,4.00)	2.66 (1.33,3.40)	2.66 (1.65,4.00)	ns p=0.105
	Finish	2.33 (1.30,3.66) ***	2.60 (1.30,4.00) **	2.33 (1.33,3.66) ***	2.00 (0.66,3.00) ***	2.33 (1.33,3.75) *	ns p=0.298
MPI - Interference	Start	1.45 (0.65,2.88)	1.90 (0.82,3.36)	1.63 (0.80,2.90)	1.36 (0.45,2.27)	1.24 (0.52,2.65)	ns p=0.103
	Finish	1.05 (0.36,2.38) ***	1.30 (0.36,2.72) ***	1.16 (0.54,2.54) ***	0.90 (0.29,2.27) *	1.00 (0.43,2.40)	ns p=0.684
MPI – Life control	Start	3.25 (2.31,4.00)	3.25 (2.00,4.00)	3.25 (2.25,4.25)	3.25 (2.46,4.00)	3.38 (2.50,4.25)	ns p=0.780
	Finish	3.50 (2.50,4.25) ***	3.50 (2.75,4.50) **	3.50 (2.50,4.00)	3.50 (2.50,4.25)	3.50 (2.50,4.25)	ns p=0.952
MPI – Affective distress	Start	3.33 (2.33,4.30)	3.60 (2.60,4.33)	3.60 (2.65,4.40)	3.00 (2.00,4.00)	3.32 (2.32,4.30)	ns p=0.063
	Finish	3.00 (2.00,4.00) ***	3.30 (2.00,4.00) **	3.33 (2.00,4.00) **	3.00 (1.92,4.00)	2.83 (2.00,3.62) *	ns p=0.590
Response of significant other							
MPI – Support response	Start	3.33 (2.30,4.66)	3.60 (2.25,4.66)	3.66 (2.32,5.00)	3.00 (2.33,4.33)	3.00 (2.00,4.33)	ns p=0.681
	Finish	3.33 (2.32,4.33)	3.33 (2.33,4.33)	3.33 (2.33,5.00)	3.00 (1.70,4.00) **	3.60 (2.17,4.47)	ns p=0.300
MPI – Punishing response	Start	1.00 (0,2.06)	0.75 (0.25,2.81)	1.25 (0.25,2.56)	0.75 (0,2.00)	0.75 (0,1.75)	ns p=0.201
	Finish	1.00 (0,2.00)	1.00 (0,2.5)	1.25 (0.25,2.00)	1.00 (0,2.00)	1.00 (0,1.75)	ns p=0.394
MPI – Solicitous response	Start	2.66 (1.50,3.87)	2.83 (1.45,3.63)	2.66 (1.77,4.37)	2.66 (1.50,3.83)	2.50 (1.30,3.83)	ns p=0.929
	Finish	2.66 (1.33,3.83)	2.50 (1.30,4.00)	2.66 (1.33,4.50)	2.66 (1.50,4.08)	2.50 (1.08,3.50)	ns p=0.798
MPI – Distracting response	Start	1.75 (0.75,2.75)	2.00 (0.75,2.75)	1.50 (0.75,3.00)	2.00 (0.75,2.75)	1.75 (0.50,3.00)	ns p=0.959
	Finish	1.75 (0.75,3.00)	2.00 (0.75,2.75)	1.50 (0.75,2.75)	1.75 (0.75,2.88)	1.75 (0.63,3.00)	ns p=0.927
Frequency of participation in							
MPI – Household chores	Start	4.80 (3.60,5.60)	4.80 (3.60,5.60)	4.80 (3.35,5.80)	4.60 (3.40,5.80)	4.80 (3.80,5.40)	ns p=0.961
	Finish	4.60 (3.60,5.60)	4.60 (4.20,5.40)	4.40 (3.40,5.60)	4.60 (3.80,5.55)	4.60 (3.60,5.60)	ns p=0.903
MPI – Outdoor work	Start	2.00 (1.00,3.00)	2.00 (1.30,3.00)	2.00 (0.88,3.10)	2.00 (0.95,3.00)	2.00 (0.85,3.00)	ns p=0.749
	Finish	2.00 (1.00,3.00)	1.78 (1.29,3.00)	2.00 (1.00,3.00)	1.80 (0.85,2.60)	2.00 (0.95,3.05)	ns p=0.687
MPI – Activities away from home	Start	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.75 (2.75,4.50)	3.25 (2.25,4.25)	3.50 (2.50,4.50)	ns p=0.714
	Finish	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.38 (2.50,4.31)	ns p=0.891
MPI – Social activities	Start	3.00 (2.30,4.00)	2.75 (2.25,3.75)	3.25 (2.50,4.00)	3.00 (2.33,3.75)	3.38 (2.00,4.06)	ns p=0.655
	Finish	3.25 (2.30,3.75)	3.00 (2.25,4.00)	3.25 (2.50,4.00)	3.13 (2.33,3.75)	3.29 (2.19,4.00)	ns p=0.498
MPI – General activity level	Start	3.38 (2.75,3.91)	3.40 (2.80,3.88)	3.44 (2.68,3.84)	3.31 (2.50,3.79)	3.34 (2.80,4.05)	ns p=0.901
	Finish	3.30 (2.76,3.81)	3.38 (2.69,3.89)	3.34 (2.84,3.83)	3.30 (2.72,3.71)	3.25 (2.83,3.81)	ns p=0.969

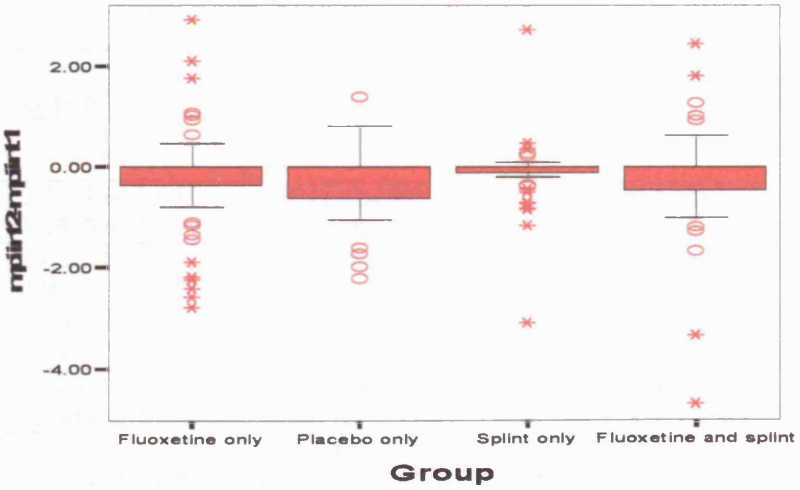
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Kruskall Wallice not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p< 0.001$

Figure 42: Patient's perspective of pain

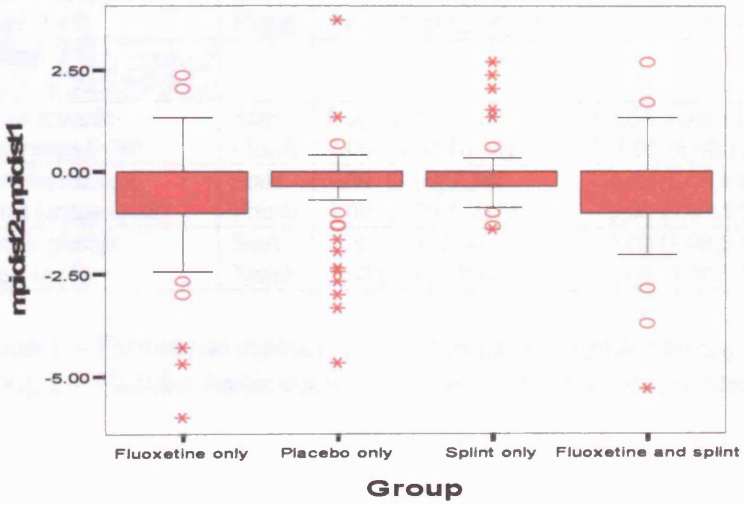
Change in MPI (severity)



Change in MPI (interference)



Change in MPI (affective distress)



Change in MPI (life control)

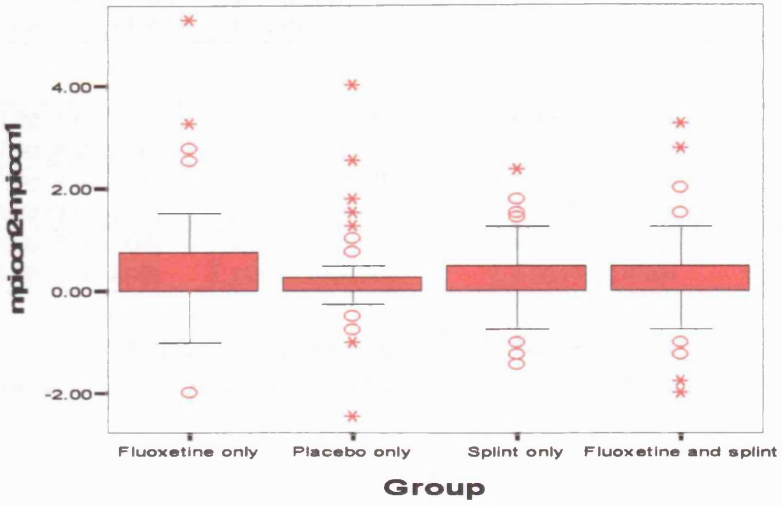


Table 32 a: McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale.(Kellner)
A comparison of median scores (25th and 75th percentiles) (Completers analysis)

Self report Questions	Study	All groups	Group 1	Group 2	Group 3	Group 4	Sig.
MPQ							
Visual analogue scale	Start	2.90 (1.20,5.45)	2.90 (1.20,6.03)	3.30 (1.60,5.60)	2.70 (1.23,4.80)	2.75 (0.90,5.38)	ns p=0.881
(VAS)(range 0-10)	Finish	2.10 (0.75,4.30) ***	2.55 (0.83,5.05)	2.20 (0.60,5.43)**	1.55 (0.48,3.05) **	2.00 (1.00,5.20)	ns p=0.564
Present pain intensity	Start	2.00 (1.00,2.00)	2.00 (1.00,3.00)	2.00 (1.00,2.00)	2.00 (1.00,2.00)	2.00 (1.00,2.00)	ns p=0.617
(PPI)(range 0-5)	Finish	1.00 (1.00,2.00) ***	1.00 (1.00,2.00) **	1.00 (1.00,2.00)*	1.00 (1.00,2.00) **	1.00 (1.00,2.00)*	ns p=0.439
MPQ – total %	Start	31.00 (20.00,47.00)	35.50 (23.50,47.00)	31.00 (19.5,40.0)	30.00 (18.00,39.50)	31.00 (18.00,50.00)	ns p=0.398
(range 0-100)	Finish	20.00 (12.00,36.00)***	24.00 (13.00,40.50) *	27.00 (13.0,38.0)*	15.50 (9.50,31.00) ***	18.00 (11.00,36.00)*	ns p=0.342
MPQ– sensory %	Start	33.00 (21.00,45.00)	39.00 (26.25,48.00)	31.00 (21.00,45.00)	33.00 (21.00,42.00)	33.00 (19.50,50.00)	ns p=0.342
(range 0-100)	Finish	24.00 (15.0,42.00) ***	31.50 (17.25,45.00) *	33.00 (18.00,45.00)	18.00 (12.50,33.00)*	21.00 (15.00,42.00)	ns p=0.278
MPQ – affective %	Start	17.00 (3.00,42.00)	25.00 (0, 52.00)	17.00 (8.00,40.50)	17.00 (8.00,25.00)	17.00 (0,50.00)	ns p=0.639
(range 0-100)	Finish	8.00 (0, 25.00) ***	8.00 (0,27.00) *	8.00 (0,25.00) **	8.00 (0,25.00) *	8.50 (0,25.00)	ns p=0.972
BDI							
Composite score	Start	7.00 (3.00,13.00)	7.00 (2.25,13.75)	7.00 (3.00,11.00)	6.00 (2.00,10.50)	8.00 (4.25,14.75)	ns p=0.344
(range 0-45)	Finish	5.00 (2.00,12.00) **	5.00 (1.25,11.75)	5.00 (2.75,10.00)*	4.00 (0.75,10.50)*	7.00 (3.00,14.00)	ns p=0.088
Kellner							
Illness attitude-	Start	8.00 (6.00,11.00)	8.00 (6.00,11.50)	7.00 (6.00,9.50)	7.50 (6.00,11.00)	8.00 (6.00,12.00)	ns p=0.206
total (range 0-30)	Finish	7.00 (6.00,10.00) *	7.00 (6.00,12.00)	7.00 (6.00,9.00)	7.00 (6.00,10.00)	8.50 (6.00,12.00)	ns p=0.147
Hypochondriacal	Start	3.00 (3.00,6.00)	4.00 (3.00,6.00)	3.00 (3.0,5.00)	3.00 (3.00,6.00)	3.00 (3.00,6.00)	ns p=0.477
beliefs (range 0-15)	Finish	3.00 (3.00,5.00) *	3.00 (3.00,5.00) *	3.00 (3.00,4.75)	3.00 (3.00,5.00)	3.50 (3.00,5.00)	ns p=0.919
Disease phobia	Start	3.00 (3.00,5.00)	3.00 (3.00,5.50)	3.00 (3.00,4.00)	3.00 (3.00,6.00)	4.00 (3.00,7.00)	ns p=0.112
(range 0-15)	Finish	3.00 (3.00,5.00)	3.00 (3.00,6.00)	3.00 (3.00,4.00)	3.00 (3.00,6.00)	4.50 (3.00,6.00)	ns p=0.085

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Kruskall-Wallis not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p<0.001$***

Table 32 b: McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale.(Kellner)
A comparison of median scores (25th and 75th percentiles) (Imputation analysis)

Self report Questions	Study	All groups	Group 1	Group 2	Group 3	Group 4	Sig.
MPQ							
Visual analogue scale (VAS) (range 0-10)	Start Finish	2.90 (1.20,5.45) 2.20 (0.80,4.95) ***	2.90 (1.20,6.03) 2.40 (0.63,4.90)	3.30 (1.60,5.60) 2.50 (0.95,5.35) **	2.70 (1.23,4.80) 2.10 (0.7,4.50) **	2.75 (0.90,5.38) 2.20 (0.95,5.95)	ns p=0.881 ns p=0.682
Present pain intensity (PPI) (range 0-5)	Start Finish	2.00 (1.00,2.00) 1.00 (1.00,2.00) ***	2.00 (1.00,3.00) 2.00 (1.00,2.00) **	2.00 (1.00,2.00) 2.00 (1.00,2.00) *	2.00 (1.00,2.00) 1.00 (1.00,2.00) **	2.00 (1.00,2.00) 1.00 (1.00,2.00) *	ns p=0.617 ns p=0.627
MPQ – total % (range 0-100)	Start Finish	31.00 (20.00,47.00) 27.00 (13.00,40.00)***	35.50 (23.50,47.00) 29.00 (17.00,45.50) *	31.00 (19.5,40.0) 29.00 (14.5,37.0)**	30.00 (18.00,39.50) 24.00 (13.00,31.00)***	30.00 (17.50,49.50) 20.00 (11.00,42.00) *	ns p=0.384 ns p=0.423
MPQ– sensory % (range 0-100)	Start Finish	33.00 (21.00,45.00) 30.00 (15.00,42.00) ***	39.00 (26.25,48.00) 33.00 (18.00,45.00) *	31.00 (21.00,45.00) 30.00(17.50,41.00)*	33.00 (21.00,42.00) 24.00 (15.00,37.50) **	31.50 (18.00,49.00) 21.00 (12.00,45.00) *	ns p=0.339 ns p=0.558
MPQ – affective % (range 0-100)	Start Finish	17.00 (0,42.00) 17.00 (0, 25.00) ***	25.00 (0, 52.00) 17.00 (0, 46.00) *	17.00 (8.00,40.50) 17.00 (0,25.00) **	17.00 (8.00,25.00) 17.00 (0,25.00) *	17.00 (0,50.00) 9.00 (0,33.00)	ns p=0.663 ns p=0.905
BDI							
Composite score (range 0-45)	Start Finish	7.00 (3.00,13.00) 6.00 (3.00,12.00) **	7.00 (2.25,13.75) 6.00 (2.00.12.50)	7.00 (3.00,11.00) 7.00 (3.00,11.00) *	6.00 (2.00,10.50) 5.00 (1.00,10.00) *	8.00 (4.25,14.75) 7.00 (3.00,13.00)	ns p=0.344 ns p=0.106
Kellner							
Illness attitude total (range 0-30)	Start Finish	8.00 (6.00,11.00) 7.00 (6.00,11.00)	8.00 (6.00,11.50) 7.00 (6.00,11.50)	7.00 (6.00,9.50) 7.00 (6.00,10.00)	7.50 (6.00,11.00) 7.00 (6.00,10.00)	8.00 (6.00,12.00) 9.00 (6.00,12.00)	ns p=0.206 ns p=0.101
Hypochondriacal beliefs (range 0-15)	Start Finish	3.00 (3.00,6.00) 3.00 (3.00,5.00) *	4.00 (3.00,6.00) 3.00 (3.00,5.00) *	3.00 (3.00,5.00) 3.00 (3.00,5.00)	3.00 (3.00,6.00) 3.00 (3.00,5.00)	3.00 (3.00,6.00) 3.50 (3.00,6.00)	ns p=0.477 ns p=0.546
Disease phobia (range 0-15)	Start Finish	3.00 (3.00,5.00) 3.00 (3.00,5.00)	3.00 (3.00,5.50) 3.00 (3.00,5.50)	3.00 (3.00,4.00) 3.00 (3.00,5.00)	3.00 (3.00,6.00) 3.00 (3.00,5.25)	4.00 (3.00,7.00) 5.00 (3.00,6.75)	ns p=0.112 ns p=0.068

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Kruskall-Wallis not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p<0.001$***

Figure 43: Amelioratin in MPQ and Kellner scores

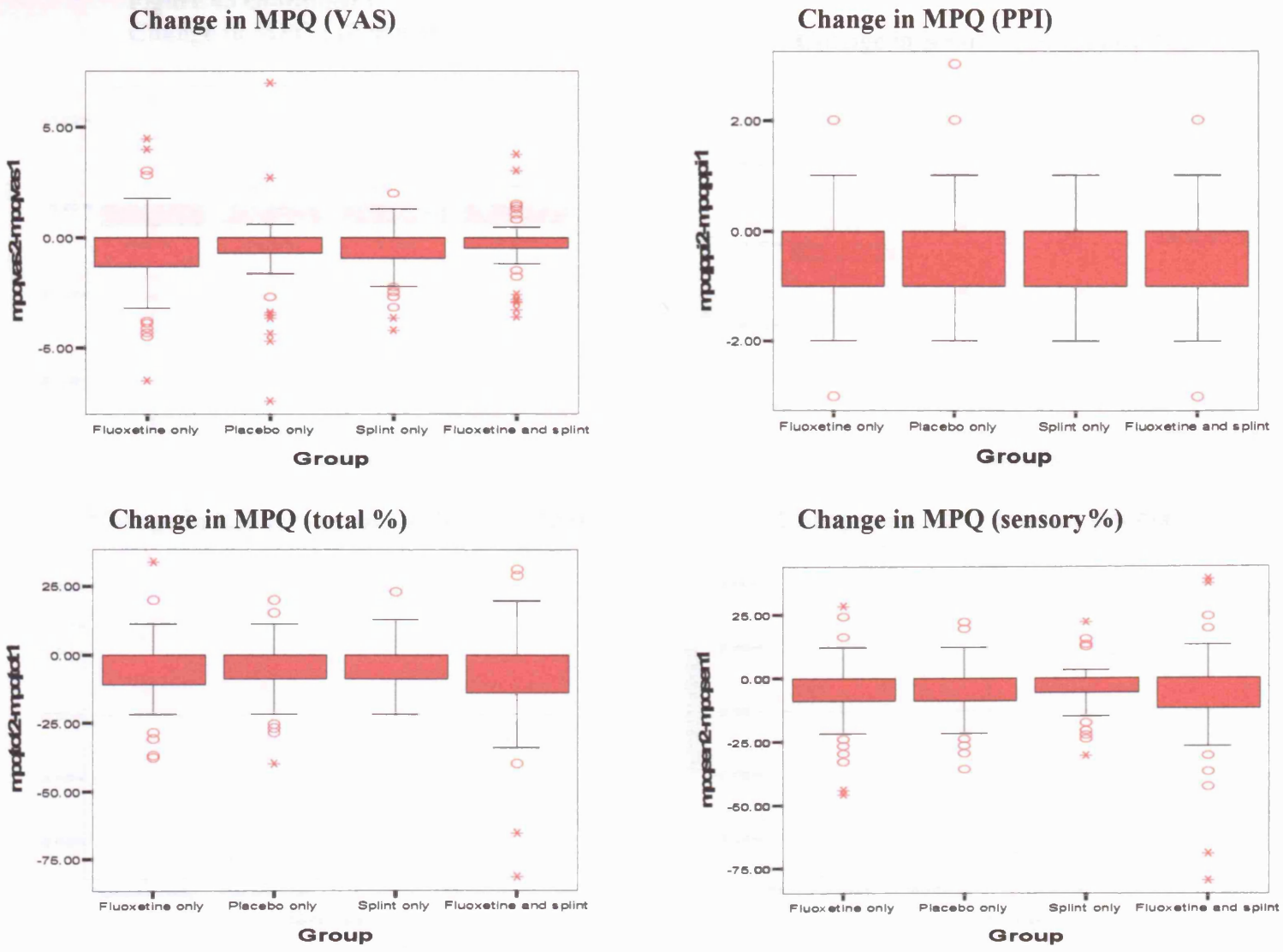
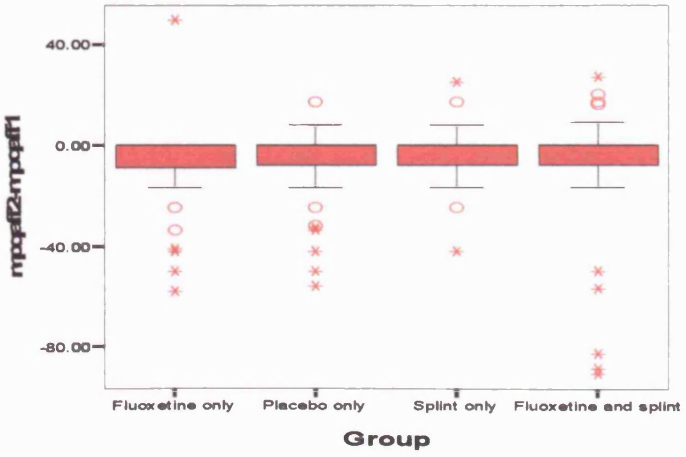
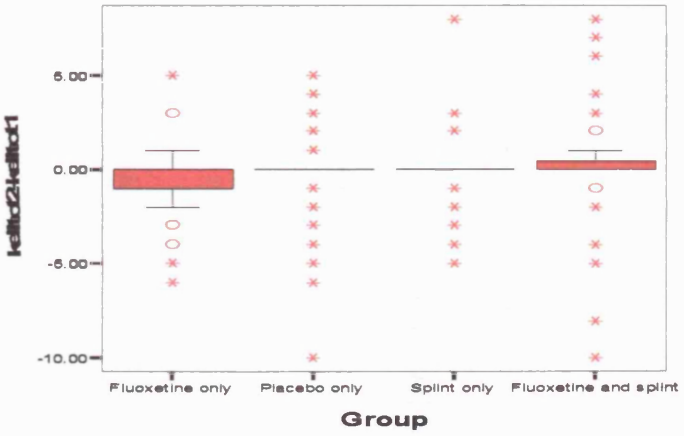


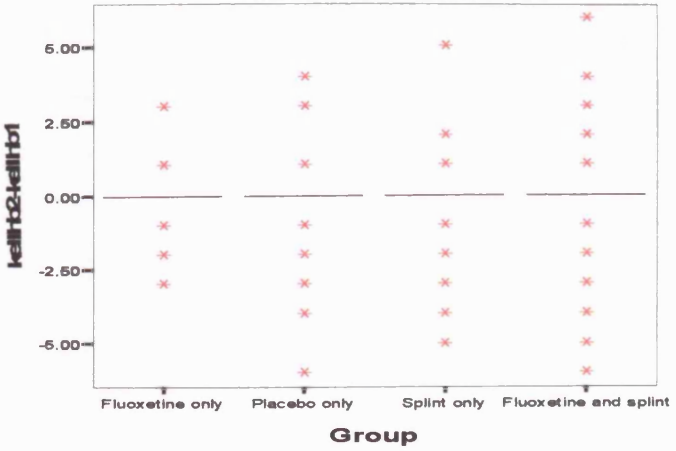
Figure 43 continued :
Change in MPQ (affective)



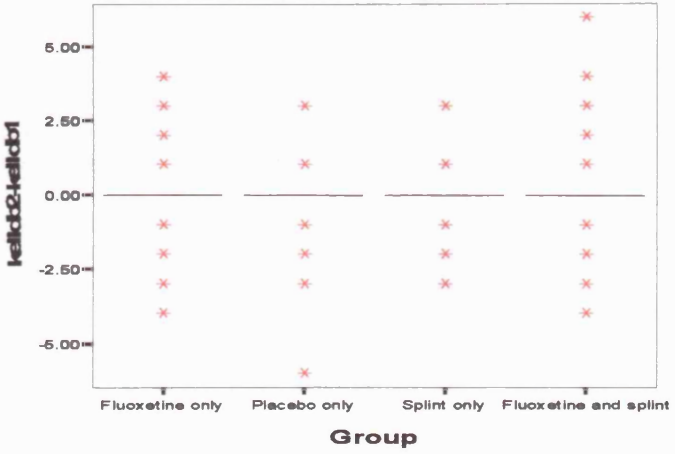
Change in Kellner (illness attitude)



Change in Kellner (hypochondriacal beliefs)



Change in Kellner (disease phobia)



7.3 OUTCOME PREDICTORS

7.3 Outcome Predictors

Bivariate analysis, using the nonparametric Spearman's Rho, identified associations between >25% and >50% pain severity improvement at the end of the trail period of three months and several initial MPI,MPQ,BDI and Kellner self reported scores.

Logistic regression analysis was then used to examine a number of these variables to see if they predict an explanatory outcome. The enter method in addition to forward and backward stepwise techniques were employed. A number of factors did remain evident in the regression analysis.

7.3.1 Summary of the Logisitic regression Analysis

Table 33: Summary of logistic regression analysis >25% improvement at 3/12

Enter method	P value	Regression coefficient	SE (standard error)	OR (Odds ratio)	95% CI (Confidence interval)
MPI (support)	0.049 *	0.233	0.118	1.262	(1.001-1.591)
MPI (outdoor work)	0.043 *	0.337	0.166	1.401	(1.011-1.941)
MPI (punishing)	0.60	-0.276	0.147	0.759	(0.569-1.011)
MPI (social activity)	0.170	0.342	0.249	1.408	(0.864-2.294)
MPI (general activity)	0.101	-0.654	0.399	0.520	(0.238-1.136)

*p<0.05

The above model accounts for 70.4% prediction of results,(χ^2 =14.710 df 5, p=0.012). In this particular study, only initially reported MPI support by significant family or friends and outdoor activity were significant predictors of improvement in pain of at least 25%..

MPI support (OR=1.26 ,95%CI 1.00-1.59, P=0.049), suggests that the chances of, at least 25% pain improvement, increase for every 1.26 unit increase in recorded level of

support. Similarly MPI outdoor activity (OR=1.40,95%CI 1.01-1.94, P=0.043), indicates that the chances of at least 25% pain improvement, increases for every 1.40 unit increase in recorded outdoor activities.

Conversely, increased recorded MPI punishing response by significant family and friends and general activity level has a negative response and social activity a positive response but this did not reach a significant level.

Table 34: Logistic regression analysis >50% pain improvement at three months

Enter method	OR (Odds ratio)	95% CI (Confidence interval)	P value	Regression coefficient	SE (standard error)
Duration (TMJ pain)	0.838	0.707-0.994	0.043*	-0.176	0.087
Backache	0.359	0.38-0.935	0.036*	-1.025	0.489
Abdominal pain	3.662	1.219-11.00	0.021*	1.298	0.561
Temporal pain	0.362	0.118-1.113	0.076	-1.016	0.573
VAS (clinical)	1.410	1.122-1.773	0.003*	0.344	0.117
VAS(MPQ)	0.820	0.667-1.007	0.059	-0.198	0.105
Kellner total (Illness attitude)	1.270	0.988-1.632	0.062	0.239	0.128
Kellner (Disease phobia)	0.636	0.407-0.992	0.046*	-0.453	0.227
MPI (punished response)	0.625	0.408-0.958	0.031*	-0.469	0.218
MPI (household chores)	0.635	0.383-1.052	0.078	-0.454	0.257
MPI (social activity)	0.368	0.178-0.759	0.007*	-1.001	0.370
MPI (generalactivity)	3.434	1.099-10.73	0.034*	1.234	0.581

*p<0.05

This model accounts for 78.5% of the 50% pain reduction χ^2 =38.177(12) P<0.001.

Several factors were found to decrease the chances of a successful 50% pain improvement at three months. These included the longer the duration of TMJ pain on initial presentation to the clinic (OR=0.84,95%CI 0.71,0.99, p=0.043), the presence of backache (OR=0.36,95%CI 0.38,0.94,p=0.036). The reporting of temporal muscle pain on presentation was again seen to decrease the chances of success but this did not reach a significant level (OR=0.362, 95%CI 0.12,1.11,p=0.07).Conversely, those reporting abdominal pain at initial presentation appeared 3 times more likely to have a 50% reduction in pain, (OR=3.66,95%CI 1.22,11.0,p= 0.021).

With regards to the self report pain questionnaires, a decreased chance of a successful outcome at three months was associated with initially reported higher score ratings in the Kellner (disease phobia) (OR=0.64, 95%CI 0.41,0.99, p=0.046), MPI (punishing response by significant family and friends) (OR=0.63, 95%CI 0.41,0.96, p=0.031), MPI (social activities) (OR=0.37,95% CI 0.18,0.76, p=0.007). Raised scores in Kellner illness attitude, MPI (household chores) and VAS (MPQ) were also negatively associated with improvement but did not reach a significant level. Conversely, pain improvement was associated with a 1.4 unit increase in initial, clinically recorded VAS (OR=1.41,95%CI 1.12,1.77,p=0.003).

MPI (general activity level) at baseline increased the chances of successful outcome for every 3.4 unit increase in initially recorded scores (OR=3.43, 95%CI 1.09,10.73, p=0.034).

An attempt was made to determine what specific factors might influence a successful therapeutic outcome in physical or medical therapy groups. Using a split file analysis no clear predictors of outcome appeared to exist solely amongst the individual groups, medical therapy versus occlusal therapy, combined therapy or indeed placebo.

VII DISCUSSION

7.4 The randomised controlled study three month treatment phase

Hypothesis (1a):

An SSRI (fluoxetine;Prozac) in daily oral doses of 20-40mg is more effective than placebo in the treatment of patients with chronic TMD.

Hypothesis (1b):

A combination of an SSRI (fluoxetine;Prozac) and a bite guard are equally effective to fluoxetine or bite guard alone in the treatment of chronic TMD.

7.4.0.1 The randomised placebo controlled trial

Randomised, placebo controlled trials are often viewed as the research 'gold standard' in the development of new treatment; measuring effect size in a scientifically consistent manner; establishing clinical sensitivity and internal validity, (Adam et al, 2005,Hauschke and Pigeot,2005, Rohmel,2005). The aim of a placebo is to control for the non-specific effects of therapy which include: statistical regression towards the mean, the natural history of the condition being treated, methodological or measurement anomalies and improvement due to psychological elements of therapy, (Kienle and Kiene,1997, Kirsch,1997, McDonald and McCabe,1989).

In recent years, since the commencement of this RCT, the role of placebo has come under close scrutiny; considered by some inappropriate or unacceptable, (Farr,2000, Weijer, 2002).Consequently, the ethical issues surrounding placebo treatment have been the topic of much discussion,(Linde et al,2003, Emanuel and Miller,2001). The 5th revised version of the declaration of Helsinki, 2000, states that "the placebo controlled clinical trials are only acceptable when no proven treatment exists for the studied disease". Therefore, trial enrolment with a placebo is only considered

legitimate when a state of 'clinical equipoise' exists; uncertainty or disagreement amongst the professional community of expert clinicians as to the preferred treatment, (Freedman,1987, Reynolds,2000).

The Note of Clarification of the Declaration of Helsinki, 2001, aimed to elucidate when trials are scientifically necessary and ethically justifiable, even when proven therapy already exists. An example would be 'to determine the efficacy or safety of therapeutic, diagnostic or prophylactic methods for a minor condition where use of a placebo will not subject the patient to additional risk, serious or irreversible harm', (WMA,2001). Clearly, no research patient should be exposed to unnecessary harm or risks of pain or suffering (Reynolds, 2000, Simon, 2000).The controversy centres around studies of non-life threatening conditions, when a delay in effective treatment is unlikely to cause harm, (Ready,2000, Vastag,2000). Placebo controlled trials are considered by some to arise from a misplaced emphasis on statistical significance testing,(Simon, 2000). However, in order for clinical research to be ethical, it must be considered scientifically valid; nevertheless, moral considerations must always take priority over the quest for scientific knowledge,(Simon,2000). Inadequate trial design is unethical since it may lead to the reporting of erroneous, inconclusive results and misleading recommendations of inconsistent or minimally effective treatment, (Weijer,2002, Power,2005).

An active control is not necessarily an alternative to an inactive placebo control, since study population inter and intra individual variation prevents direct comparison or equivalence with historical controls,(Linde et al,2003).Use of an active –control, where a new agent and an active control are shown to have similar efficacy, is a non inferiority response and is therefore a less scientifically reliable design than superiority trials with either an active or in-active comparator, (Emanuel

and Miller,2001, Reynolds,2000).However, a similar response with an active control but no placebo does not necessarily prove efficacy in a particular population or experimental group beyond the natural course of the condition, (Emanuel and Miller,2001). Where the effectiveness of available active treatment is mild or variable compared to new treatment, superiority over placebo is the only scientific way to establish efficacy, (Reynolds, 2000,Vickers, 2000).Therefore, incorporating a placebo group clearly increases scientific credence of the study population. Placebo controlled trials are considered to have a sound scientific rationale when: the studied population has a high placebo response rate; the condition is typically characterised by a remitting course with frequent spontaneous remissions and existing therapies are only partially effective,(Emanuel and Miller,2001).All these specified criteria are fulfilled within the study of TMD.

Ideally a new drug should be tested against both placebo and active control, in a three armed study design,(Temple and Ellenberg, 2000). This particular research study was in fact a four armed design which provides scientifically valid information on the two treatments under investigation drug and splint alone and in combination versus placebo. Would a trial of this design be prohibited in the future? Within TMD, placebo groups may be considered unethical because simple treatments have proven beneficial for many TMD patients; however, placebo controlled trials are useful for determining the most appropriate treatment for the varied TMD subgroups who do not respond to standard treatment (Dworkin et al, 2002c).

When considering TMD, although a range of therapies are currently employed, a state of 'clinical equipoise' does exist with regards to the most appropriate form of treatment for this condition and its subgroups; hence justifying the need for RCT's in this particular field, (Dworkin and Drangsholt,2005).

7.4.0.2 Study participation and informed consent

Informed consent was obtained from all patients prior to enrolment in treatment. The motivation for patients entering trials is predominantly personal benefit rather than altruistic or scientific in origin (Edwards et al,1998, Farr,2000). Patients usually trust and depend on the clinician for advice and treatment; an equipoised RCT may therefore seem contrary to their expectations of care,(Linde et al,2003). 'Randomisation' and 'double-blinding' can be difficult concepts for the patient to grasp,(Corbett et al,1996, Stead et al,2005). Therapy, within a RCT, is no longer the informed decision of the patient guided by the clinician but instead a chance allocation not directly under the clinicians control,(Turney,1996, Joffe et al,2001). This could lead to a lack of confidence in care and difficulty in acceptance of treatment within the trial,(Corbett et al,1996, Edwards et al,1998). To allay this fear requires a certain level of communication; the quality of communication between the patient and the clinician obtaining consent is fundamental in gauging the patients level of understanding and acceptance of treatment,(Stead et al,2005). National guidelines on written information for trial participants now exist which should be pre-tested to ensure readability,(Adam et al,2005). The written information sheet must provide a realistic view of the study without being over optimistic or provoking undue concern,(Stead et al,2005). Qualitative studies of the patients understanding and perspective of clinical trial information showed that what may appear objective and unambiguous to the clinician can still be misinterpreted by a patient with limited scientific knowledge and variable levels of understanding, often compounded by emotional stress associated with the decision of whether to participate in an experimental trial (Edwards et al,1998, Stead et al,2005). Clinicians sometimes underestimate the patients need for detailed information, yet conversely

too much information can increase anxiety and reduce willingness to participate in a study, (Edwards et al,1998, Emanuel and Miller,2001). This in part is perhaps explained by the patients' internal or external health locus of control.

The role of the clinician within a trial is, first and foremost, to protect the welfare of the patient; the task of physician and healer taking precedence over the role of researcher and scientist,(WMA,2000). Therefore, informed consent is essential, in all realms of treatment but particularly in clinical studies, to ensure the subject understands the implications of participation as an individual and as a 'co-adventurer' in the prospective research,(Thornton,1995,Linde et al, 2005). Patients, before embarking on treatment and when participating in the clinical trial were clearly informed they were under no obligation to complete the study but could withdraw at any stage, a standard pre-requisite for clinical research, (Linde et al,2003). This obviously results in the potential for individual deviation from the study protocol, leading to non-adherence, withdrawal from study participation and drop-out, which will be discussed in Chapter IX.

7.4.1 Treatment outcome

Treatment outcome was assessed when possible using the recommended intention to treat analysis (ITT), Altman et al,2001. This is a means whereby all randomised subjects are analysed according to their original treatment group, whether or not they completed the treatment intervention. ITT analysis provides a conservative measure of treatment effect and prevents potential bias by maintaining all subjects with baseline equivalence at random allocation,(Altman et al, 2001).

In contrast, analysis of only complete cases is problematic since the decreased sample size causes loss of power. Therefore, analysing data only from patients

adherent to the assigned treatment regimes is unreliable and may be misleading, (Knatterand,2002,). The literature suggests this type of assessment only gives a clinical indicator for the possible success in an individual compliant patient. Therefore, when data is missing an imputation analysis is required in order to account for the missing variables.

Last-observation-carried-forward (LOCF), a form of imputation analysis, is frequently employed,(Altman et al,2001). However, it has disadvantages of bias due to imputed values having no variability and perfect correlation hence actually underestimating variability in the data set and reducing the chances of observing a marked effect, (Peduzzi et al, 2002).

An imputation analysis, last score brought forward, was undertaken but compared to the pragmatic, completers analysis. As a sensitivity analysis both sets of results were compared but did not show any remarkable differences or variation in outcome and significance.

7.4.1.1 Primary outcome measures

A favourable outcome in treatment response was recorded for all therapeutic groups. Improvement in >50% and >25% pain relief on the 10cm VAS was observed for each treatment group but there was no significant difference between groups, (tables 19, figures 31). A combination of an SSRI (fluoxetine:Prozac) and a bite guard therefore appear equally effective to fluoxetine or bite guard alone in the treatment of chronic TMD.

However, a significant difference was observed between SSRI and placebo at >50% pain relief in the ITT and completers analysis. An effect size of 2.07 (CI 1.16-3.70) for the ITT, (N=201) and 1.84 (CI 1.05-3.24) for the completers analysis, (N=165).

These results suggest approximately twice as many patients improve with SSRI compared to placebo, indicating that an SSRI (fluoxetine:Proazac) in daily oral doses of 20-40mg may be more effective than placebo in the treatment of patients with chronic TMD.

This finding was only observed at >50% improvement in pain scores. The more generalised improvement of >25%, perhaps more readily attainable by study subjects, was not statistically significant between SSRI and placebo. This might suggest the SSRI was effective in producing a marked reduction in pain levels for a particular subgroup of the population and therefore merits further investigation.

7.4.1.1.1 Numbers needed to treat analysis

The results suggest that for every 100 TMD patients who commenced treatment, >50% pain relief could be achieved in (100/4.1) 24 with fluoxetine,(100/14.8) 7 with a bite guard and (100/7.8) 13 with fluoxetine and biteguard. For every 100 TMD patients >25% pain relief could be achieved in (100/5.6) 18 with fluoxetine, (100/13.1) 8 with a bite guard and (100/5.8) 17 with both fluoxetine and biteguard. One might have hoped that results would indicate a synergistic therapeutic effect with the dual treatment but this was not apparent. The NNT was most favourable for the SSRI medical therapy group. Although the NNT values are not within the ideal range of 2-4, an NNT of 4.1 for >50% pain relief or 5.6 for >25% pain relief, compares very favourably to previous studies of SSRI's in chronic pain suggesting an NNT of 6.7,(Chang,2005).

Moore,1999, suggests that in acute pain trials in order to achieve a 'clinically credible' NNT result in terms of 'magnitude'of analgesic efficacy, 500 patients per group are required not the more conventional 40 patients per group, since NNT

values between 1-9 may otherwise occur by chance. Although this study deals with chronic pain, random chance may still be an issue.

Another error to consider in the trial methodology is whether the initial (VAS) pain severity was of a significant level to enable assessment of analgesic efficacy. Including patients with only moderate to severe pain intensity at baseline and excluding those with mild or no pain optimises trial sensitivity but cannot allow for natural fluctuation in levels of pain intensity over time and regression towards the mean. What is considered moderate pain on a VAS? Collins et al,1997, suggest that when patients record a baseline severity score in excess of 3cm, on a VAS, this probably relates to at least a moderate level on a categorical scale. The VAS severity recordings, used to calculate the NNT, complied with this recommendation. At baseline clinical consultation, patients asked to indicate on a VAS the severity of their pain consistently recorded a mean 5-6.3cm.

However, on examining the patient self-reported MPQ VAS in the baseline McGill pain questionnaire, completed prior to consultation, median pain scores are recorded below the mandatory 3cm in all groups. If patients were in fact experiencing levels of current pain below 3cm, suggesting mild pain, the actual measurement of pain at baseline and description of treatment efficacy becomes problematic. Indeed, repeating the NNT with the MPQVAS, as opposed to the VAS severity used in the earlier calculations, produces no meaningful results. Guidance was given by the clinician on completing the VAS severity. In contrast, although instructions were provided for completing the VAS on the MPQ, these recordings were completed without supervision which may give rise to initial erroneous reporting (Scott and Hutchinson,1979). It has been noted that a VAS may be difficult for patients to complete when first encountered, (Downie,1978).

Another issue to consider, is whether patients should be shown their initial pain rating when reassessing pain at review appointments,(McDowell and Newell, 1987). The accuracy with which an individual can recall an original pain score from memory varies according to the placement of the original mark at the centre or the extremety of the line, (Dixon,1981).

Patients in this RCT completed the VASMPQ after a three month gap without visible knowledge of the original scores. Scott and Hutchinson,1979, suggest patients should be shown their previous scores when the length of time between assessments may lead to the patients having difficulty in recalling their initial scores hence reducing the validity of comparing scores before and after treatment. Nevertheless, the VAS is a standard tool for the assessment of pain. The recordings taken at the regular monthly intervals on the VAS severity scale, as opposed to the VASMPQ, were therefore considered the most valid for the measurement of effect size and NNT.

7.4.1.2 Secondary outcome measures

Hypothesis (4a): A significant improvement in the 'clinician recorded' intensity, interference and frequency of patient TMD pain, is only observed in the dual therapy group.

7.4.1.2.1 Pain severity and intensity

Pain severity was measured using the VAS (1-10cm line). General severity scores showed a significant and consistent reduction regardless of therapeutic intervention $p<0.001$. This was similarly seen in pain intensity.

7.4.1.2.2 Frequency and interference with life

Frequency and interference with life again showed significant improvement over the time course of the study independent of the treatment provided. This would be consistent with the observed reduction in pain severity and intensity.

Hypothesis (4b): A significant improvement in the 'self recorded' impact of TMD pain on daily life; MPI severity, interference, life control and affective distress is only observed in the dual therapy group.

7.4.1.2.3 Mutidemensional pain inventory (MPI)

MPI results showed no significant differences between groups at three months.

Examining the entire cohort as a single group analysis showed overall improvement in the patients perspective of pain $p<0.001$ in severity, interference, life control and affective distress.

Examining each group individually intra group analysis reveals reduced pain severity, greatest amongst group 2 and group 3 $p<0.001$, group 1 $p<0.005$ and group 4 $p<0.05$.

Interference was reduced in group 2 $p<0.001$ and group 1 and group 3 $p<0.05$.

Life control was improved in group 1 $p<0.005$, group2 and group 3 $p<0.05$ whilst affective distress was reduced in group 2 $p<0.001$ and group 1 and group 4 $p<0.05$.

7.4.1.2.4 MPQ

Results were significantly reduced when examining all groups $p<0.001$. In intra group analysis MPQ and PPI was significantly reduced in group1 and group 3 whilst VAS was significantly reduced in group 2 and group3. However, there was no significant difference between the four groups.

Hypothesis (4c): There is a significant difference in 'self recorded' BDI depression scores between the commencement and completion of the study.

7.4.1.2.5 Depression

Interestingly it is the placebo and splint alone groups who showed significant reduction in depression scores $p<0.05$. However, this must be considered, in the light of the fact, that median scores are already below those indicative of mild depression.

Hypothesis (4d): There is a significant difference in 'self recorded' Kellner illness attitude and beliefs between commencement and completion of the study.

7.4.1.2.4 Illness attitude

Hypochondriacal beliefs alone were seen to reduce in the Fluoxetine only group $p<0.05$ which might be related to the effect this type of drug has on the individuals affect.

7.5 Clinical outcome measures

7.5.1 Interincisal mouth opening

The measurement of mouth opening and range of movement is limited by the patient's subjective interpretation and awareness of associated pain. However, maximal assisted jaw opening reduces the patients subjective component and is therefore considered an objective measure, (Stegenga et al,1993).Parametric statistics were therefore employed and revealed a statistically significant linear improvement in mouth opening at all four time points for both completers and imputation analysis, $F(2.3)=6.57, p=0.001$ and $F(2.4)=3.69, p=0.018$ respectively.

An improvement of 2.81mm was observed in the completers analysis (n=165) and 1.38mm for the imputation analysis (n=250).Although statistically significant this may not be a clinically meaningful change.

Interestingly, intra group analysis suggested the SSRI group and SSRI with splint groups did not appear to improve significantly over 12 weeks in the completers analysis p=0.167 and p=0.701 respectively, whilst improvement was noted in placebo and splint only groups p=0.007 and p=0.028 respectively. However, inter group analysis was not significant so no assumptions can be drawn from these findings.

Hypothesis (5a): There is a significant improvement in the signs and symptoms of TMD between the commencement and completion of the study.

Hypothesis (5b): A significant improvement in the signs and symptoms of TMD are only seen in those wearing a bite guard.

7.5.2 TMJ signs and symptoms

A significant reduction in reported TMJ pain $p<0.001$ and muscle discomfort $p<0.05$ were recorded for all groups. Inter group analysis showed a significant reduction in masseter muscle pain, ($p<0.05$) in the splint therapy group which remained significant in the between group analysis (p=0.008).This concurs with previous studies showing a significant reduction in tender masticatory muscles with the use of stabilization appliances (p=0.018),(Ekberg et al, 2003).This may indicate a true reduction in muscle pain as a result of the splint therapy. Conversely it may relate to an increase in muscle pain related to the medical therapy group due to the possibility that SSRIs may increase the level of bruxism and insomnia so aggravating TMD.

The character of pain notably dull ache and sharp episodes also decreased significantly in all groups, ($p<0.001$).However, patients continued to describe symptoms of TMJ and muscle pain throughout the course of the study which reinforces the concept of whether results can be considered clinically meaningful. Perhaps patients although aware of symptoms, no longer experienced a 'dyfunctional' TMJ but could now be classified as 'functional', having reached a point of symptom tolerance where, despite mild symptoms, there was less significant interference with daily activities of social functioning notably eating, chewing, talking and yawning.

7.5.3 Orofacial pain

In contrast, increased pain was related to the face,($p=0.002$), ears,($p=0.003$) and teeth,($p=0.019$) were noted in the splint therapy group which remained significant between groups. This might relate to an increased focus on the occlusion and an awareness of the face, preauricular region of the ear and teeth whilst wearing an occlusal appliance.

Hypothesis (5c): There is a significant difference in the number of co-morbid pain conditions reported between commencement and completion of the study.
Hypothesis (5d): A significant improvement in co-morbid pain conditions is only seen in those taking SSRI (fluoxetine).

7.5.4 Chronic recurrent pains

Headache, migraine, neck ache, backache and abdominal pain all decreased significantly during the course of treatment, ($p<0.001$). In chapter VI, comment was

made of the high level of concomitant headache (61%), neck ache (50%) and backache (48%) amongst study participants. There is evidence to suggest patients with TMD and multiple chronic pain conditions are more psychologically distressed, (LeResche et al,1987, Dworkin et al,1990). Such patients may also be more prone to develop long term TMD with pain related disability and persistent pain, (John et al,2003, Rammelsburg,2003).This may indicate that patients with multiple co-morbid pain conditions would have been more recalcitrant to therapy particularly a simple physical occlusal appliance. However, the patients in this RCT appear to have responded favourably to a decrease in co-morbid pain conditions regardless of therapeutic intervention. It would be interesting to observe long-term, whether the decrease in co-morbid pain conditions was simply a transitory phenomena, for the duration of study participation.

7.6 Overall outcome

In relation to hypothesis 1a; An SSRI (fluoxetine; Prozac) in daily oral doses of 20-40mg has been found to be more effective than placebo in the treatment of patients with TMD.

In relation to hypothesis 1b; A combination of an SSRI (fluoxetine;Prozac) and a bite guard have been found to be equally effective to fluoxetine and bite guard alone in the treatment of chronic TMD.

Initially it had been proposed that group 4, the splint and drug combination, would provide the most comprehensive treatment. Increased therapeutic content provided by two clinicians could theoretically have resulted in higher levels of improvement, There was no difference between groups in the majority of primary and secondary outcome measures. The placebo often appeared equally effective to the dual therapy.

In TMD, it has been shown that conservative advice and reassurance is responsible for improvement or resolution of symptoms in 40% of the population,(Wright and Schiffman, 1995).The results of this study may therefore simply reflect a generalised improvement following informed and explanatory reassurance of the nature of the pain condition at the initial consultation. If reassurance alone was responsible for improvement, one might wonder why patients would have entered into the inconvenience of attending a study. The patients who entered treatment may have sought reinforcement of the therapeutic alliance with regular clinical appointments within a hospital environment, which in itself could be viewed as a therapeutic intervention or an element of the placebo phenomena. Improvement in pain may also reflect a general improvement due to the satisfactory completion of the treatment intervention. It may not necessarily be the prescribed treatment that is important but unknown confounding factors, the manner, environment or mere provision of treatment that is important, reinforcing the concept that treatment approaches may be variable provided they remain reversible and non-invasive.

Overall, regardless of therapeutic intervention, there was a significant reduction in pain scores, primary and secondary outcome measures, over the trial period. This may imply that all patients improve regardless of therapy and may simply reflect a natural regression towards the mean, (Whitney and Von Korff, 1992). If this were the case, then one might consider whether the therapeutic intervention plays any active role in the improvement observed or could the patients simply have been observed over the study period. In order to confirm this hypothesis a group receiving no therapeutic intervention, a waiting list group, could have been included. However, such an approach was not thought appropriate and could be deemed unethical when considering the evidence suggesting that the sooner chronic pain is

treated , the greater the chances of a successful therapeutic outcome. However, the high level of placebo response observed in this RCT is not unusual.

7.7 The placebo effect

The placebo response is often observed but varies considerably between clinical trials; the high correlation of medication and placebo response frequently causes difficulty in proving superior efficacy of the study drug, (Walach et al, 2005). One third of published trials of antidepressants in the treatment of depression fail to demonstrate efficacy,(Thane,1999).

The placebo response in relief of chronic pain is reliant on the phenomena of regression towards the mean, the natural history of remitting and fluctuating symptom levels together with the sensitivity of patients to the encouragement and nurturing received during treatment,(Kienle and Kiene,1997, Kirsch,1997, McDonald and McCabe,1989).

Kaptchuk et al, 2006, suggests not all placebos have equivalent effect but vary depending upon the clinical environment and 'behaviours embedded in the medical ritual'. Neurobiological, psychosocial and psychodynamic mechanisms of the placebo effect are gradually being unravelled,(Colloca and Benedetti,2005, Wager et al,2004, Pariente et al,2005, Mayberg et al,2002).The diverse range of empirical factors are too numerous to list but tangibly may include: appearance, attitude and seniority of the clinician together with the placebo treatment received; colour of tablets, expected side effects, use of sham needles, technical equipment or surgical intervention,(Kaptchuk et al,2006).

The use of the placebo controlled trial was also considered to be the major influence on drop-out in antipsychotic drug trials prompting consideration of alternative

designs, (Kemmler et al,2005). To reduce the placebo effect in depression and increase the power of trials it is suggested recruiting only subjects with moderate and severe illness and incorporating a four week lead in phase with patient education on depression to reduce the placebo response once the trial begins. A pre-randomisation placebo run-in period has been used in an attempt to exclude poor adherents,(Davis et al,1995). The participants for the potential clinical trial were considered poor adherents if they took less than 80% of their medication and were mainly identified amongst the less educated population. However, placebo run-in had a negative effect on recruitment with little effect on outcome and was not recommended for highly educated participants.(Davis et al 1995).

Improvement during placebo treatment appears to be attributed to the non-specific factors of clinical trial participation rather than taking medication as recorded in a study evaluating the effect of placebo versus no treatment during a hypnosis trial (McCall et al, 2005). A three arm clinical study including an active control group is recommended to demonstrate superiority of active reference and experimental treatment over placebo,(Hauschke and Pigeot,2005).

Desbiens,2002, suggests more effort should be made in studies to ensure placebo treatment cannot be distinguished form active treatment. Walter et al, 2005 undertook pre-trial evaluation of potential un-blinding of medication by determining if tablets could be differentiated by taste and appearance. Taste was not significant but texture, colour and shape of tablets showed borderline significance although tablets were compared simultaneously side by side which is unlikely to occur in a parallel group drugs trial. The placebo treatment in this study was identical in appearance, colour and texture to the active drug treatment.

Ernst and Resch,1995, indicates that within clinical trials a mixture of true and false

placebo responses exist. The true placebo effects may be due to 'the meaning of an intervention' for a particular patient and the resultant therapeutic effect, (Moreman and Jonas,2002). Therapeutic effects of treatment may be considered a 'meaning effect' when complex interactions occur within an individual to induce healing, (Moreman, 2002). The individual attempts to construct meaning out of their medical condition, therapeutic intervention and accompanying psychological state with observed alteration in brain function (Wagner et al,2004, Pariente et al,2005). Hrobjartsson, 2002, indicate that the true placebo response rate of a RCT can not be measured when a natural control group is absent. Incorporating a third component: treatment, placebo and natural history control group found no significant difference for dichotomous variables but a significant effect size for continuous measures reflecting the placebo effect in pain, (Hrobjartsson and Gotzche,2001). Although a waiting list group is sometimes recommended this was not employed in this study since withholding any form of treatment seemed unethical.

The components of the placebo effect have only been analysed in a few clinical trials (Amarzio et al,2001, Vase et al,2003). Indirect secondary analysis of published trials was undertaken to investigate the study characteristics which contribute to placebo response rate in RCT's,(Walach et al,2005). Walach and Maighof,1999, analysed 26 RCT's of treatment duration of 12 weeks or greater and found a significant correlation between placebo response rate($r=0.59$). In studies of antidepressants there was an even higher correlation between treatment and placebo group ($r=0.9$),(Kirsch and Sapirstein,1998 cited in Walach, et al,2005). These findings were replicated in an analysis of SSRI's, using licsensing data, which found that 82% of the drug effect was in fact replicated by placebo, (Kirsch et al,2002, cited in Walach et al,2005).

Expectations and cognitions of the clinician and patient may influence response rate in addition to the investment of time, effort and involvement of staff within the study and direct patient contact. Walach et al 2005, conducted a systematic review of published data to determine if the placebo rate in RCT's was dependant not only on quality and length of study but also a range of further characteristics including organisational aspects, methodology including unblinding, time and intensity of patient contact and attitude of investigators towards the study.The duration of the studies were all chosen to encompass an appropriate time period of natural fluctuation. Placebo improvement rates were significantly correlated to improvement rates in treatment groups r=0.78 , in duration of study r=0.41 and in preventative trials r=0.59. Methodological quality including unblinding did not appear to be correlated. The non-specific effects of treatment were therefore found to be more important than the specific effects of treatment as also noted in previous studies, (McQuay,1996, Vase et al,2003, Walach and Jonas,2004).Walach ,2005 found that non specific effects of treatment accounted for 60% of the variance in treatment effects; natural history of the condition under study or general cohort effects perhaps explaining the high correlation. In a subsidiary analysis an even higher placebo response rate was noted in studies of antidepressants and anxyolitics.

Clearly from the literature, a wide variability in placebo response is frequently a feature of pain studies, (Ware,1993). Kirsch and Sapirstein,1998, in a meta analysis of 19 trials using fluoxetine, calculated that the placebo affect accounted for 50% of the observable improvement. Earlier, in the 1980's a series of meta analyses for a quality assurance programme of antidepressants in mental disorders found that placebo accounts for 60% improvement in depression, 53% in anxiety disorder, 23% in agoraphobia and 21% in obsessive compulsive disorder,

(Andrews,2001). Walach et al, 2005, suggests the placebo response rate reflects a genuine improvement and accounts for nearly 60% of the variance of all treatment effects. They found study characteristics notably methodological anomalies and diagnoses treated partly explain the placebo response but significant positive predictors of the placebo response include: preventive trials, duration and quality of study, (Walach et al,2005). It appears the placebo response increases for longer studies and those of better methodological quality whereas a decreased response is seen when dropouts and additional treatment have not been documented,(Walach et al,2005)

The large placebo response is clearly a major confounding factor for research drug trials (Enserink,1999).The extent of the placebo response although perhaps problematic in research could be beneficial for general treatment. When analysing studies that maximise the placebo effect there was a much greater effect size (d=0.95) compared to those using placebo merely as a control measure (d=0.15), (Vase et al, 2002). Rather than being viewed as a hindrance, potentiation of the placebo effect, by simple psychological strategies, could be utilized in the clinical setting to optimise patient care,(Andrews,2001).

7.8 Sleep

Sleep is an essential element to an individuals feeling of well being with disturbance of sleep patterns causing fatigue, worsening pain and aggravating depression, (Brousseau et al, 2003, Arnow et al, 2006).

From animal studies it has been noted that Fluoxetine suppressed REM (rapid eye movement) sleep; cats became irritable and hostile during REM sleep after several days of receiving fluoxetine, decreasing with continued treatment and disappearing

on cessation of the drug, (Slater et al, 1978). In human clinical trials, sleep again appeared to be the only symptom where improvement with Fluoxetine was not significantly superior to placebo at the end of the study. Meanwhile, the tricyclic antidepressants, such as imipramine, were significantly superior in relation to sleep patterns compared to fluoxetine, (Cohn and Wilcox,1985). The effect on sleep clearly varies between antidepressant classes, (Mayes and Baldwin, 2005, Lam, 2006). The lack of sedative action in relation to fluoxetine, causing an alerting or insomniac effect, is well known although equivocally some patients do report tiredness, (BNF, 2006).

However, one could suggest that perhaps the key factor with regards to sleep disturbance in the use of fluoxetine, is the alteration of the sleep pattern. From EMG studies of the TMJ masticatory function it is clear that nocturnal bruxism occurs during sleep, (Dahlstrom,1989, Lavigne et al, 1999). Any agitation during this time, could hypothetically, therefore, increase the level of grinding and tooth clenching, in fact exacerbating the TMJ condition. This could therefore begin to explain the observed and unexpected lack of clear improvement in the SSRI and SSRI and splint groups. It is feasible that the drug was inadvertently aggravating the neuromuscular grinding habit during sleep especially during the initial stages of usage. Such supposition would require controlled sleep studies with Fluoxetine or SSRIs, TCA's and placebo to monitor masticatory muscle activity during sleep.

7.9 Outcome predictors

Performing a logistic regression analysis of outcome predictors it was hoped to establish a model to account for pain improvement >25% and >50% at three months (table 68,69). Pain improvement of 25%, was related to MPI support by significant

family or friends OR=1.26 (CI 1.00,1.59) p=0.049 and outdoor activity OR =1.4 (CI 1.01-1.94) p=0.043. Support by others is clearly an important facet of pain management as found in previous studies (Newton-John, 2004).Outdoor activity is an interesting finding suggesting fresh air exposure and exercise. This will no doubt to some extent be seasonally dependant on the weather and may, therefore, additionally act as a confounding factor in the course of the study.

Pain improvement of greater than 50%, was associated with a more comprehensive model of factors. A decrease in successful outcome was related to several factors including: the duration of TMJ pain at presentation to the clinic; the presence of additional chronic recurrent pains (backache, abdominal pain and temporal pain); high scored ratings in Kellner (disease phobia) and MPI (punishing response and social activity level). Increase in VAS and general activity level at baseline improved the chances of a successful outcome OR=3.43 (CI 1.09,10.73) p=0.034.

In an attempt to analyse the study cohort in more depth, in the following chapter, subgroup analysis will be explored. Groups will be examined in relation to the initially depressed and non-depressed, initially high and low pain scores and responders and non-responders to therapy to see if patterns of improvement were evident or established between particular groups.

8.0 SUB- GROUP ANALYSIS

CHAPTER VIII STUY COHORT – SUB GROUP ANALYSIS

Hypothesis (6a) , (6b), (6c)

(6a) A significant and measurable improvement in pain is only seen in those patients without depression at baseline.

(6b) A significant and measurable improvement in pain measures are only seen in those patients with initially high pain scores

(6c) Clinical and pain history characteristics at baseline separate the treatment responders from the non responders

8.0 Subgroup analysis

Subgroup analysis was performed to investigate whether there was any difference between the initial demographics, clinical history , examination and pain questionnaire scores in responders(>50% pain improvement) and nonresponders to therapy, (<50% pain improvement).

Demographics and outcome response in those who initially had high depression scores (BDI score >9.00) and high pain scores (MPI severity scores >3.00) were examined to determine if this influenced outcome measures.

The three subgroups to be analysed:

The effect of depression on outcome measures **(section 8.1)**

The effect of initially high pain scores on outcome **(section 8.2)**

The difference between responders and non-responders **(section 8.3)**

8.1 THE EFFECT OF DEPRESSION ON OUTCOME MEASURES

8.1.0 The effect of depression on outcome measures

Hypothesis (6a) A significant and measurable improvement in pain is only seen in those patients without depression at baseline.

8.1.1 BDI scores at baseline

The baseline BDI scores of depression were non parametric, with the distribution curve skewed to the left,(figure 44). The majority of patients were clinically non-depressed with a median score of 7.00 (25^{th} and 75^{th} percentiles 3.00-13.00).

Using non-parametric bivariate correlation, significance was established at the 0.01 level, with a number of variables. Unexpectedly, the duration of pain did not correlate with depression (p=0.535).

A positive correlation at the 0.01 level was observed at baseline between: age, r =0.189 (p=0.003), MPQ: VAS (r = 0.228 p=0.001), PPI (r =0.228 p =0.001), total% (r = 0.402 p <0.001), sensory % (r = 0.355 p<0.001), affective % (r = 0.426 p<0.001), Kellner: illness attitude (r = 0.364 p<0.001), hypochondriacal beliefs (r=0.314 p<0.001), disease phobia (r = 0.317 p<0.001), MPI : pain severity (r = 0.313 p<0.001), interference (r = 0.467 p<0.001),affective distress (r =0.533 p<0.001) and punishing response (r =0.320 p<0.001)

A negative correlation at baseline was observed between BDI score and MPI activities away from home (r = -0.262,p<0.001), social activities (r = -0.197, p=0.003) and life control (r = -0.491 p<0.001).

8.1.2 BDI scores at three months

After treatment at three months again a positive correlation was observed between BDI score at baseline and the MPI scores at three months: severity (r=0.271, p<0.001),

interference (r=0.426,p<0.001), affective distress (r=0.446,p<0.001), punishing response (r=0.352,p,0.001), household chores (r=0.128,p<0.05), outdoor work (r=0.148,p=0.03) with a negative correlation between BDI score at three months and MPI activities away from home (r=-0.185,p=0.004).

A positive correlation was found with MPQ: VAS (r=0.256,p<0.001),PPI (r=0.025,p<0.001), total (r=0.314,p<0.001), sensory (r=0.261,p<0.001), affective (r=0.428,p<0.001), Kellner: total (r=0.425,p<0.001),hypochondriacal beliefs (r=0.377,p<0.001), disease phobia (r=342,p<0.001).Similar correlations were also found with the BDI scores recorded at three months.

8.1.3 BDI categorised into depressed and non depressed subgroups

Although there is a significant (p<0.005) amelioration in BDI rating at three months, there are clearly a number of outliers,(figure 45). To examine this broad variation, BDI scores at baseline were first categorised into levels of depression (scores 0-9 none, 10-14, borderline, 15-20, mild, 21 or above severe),(figure 46).There was no significance in the distribution between therapeutic groups χ^2 =1.272(3),p=0.736,(table35).

This was further dichotomised into depressed (n=84) and non depressed (n=153), with no significant difference between groups χ^2=2.313(3),p=0.510,(figure 47).

These two categories were then analysed to determine the significance of depression in relation to a series of reported variables. These included; demographic details, sleep disturbance and prevention, emotional factors influencing pain, reporting of chronic pains and treatment, outcome variables, self reporting scales and pain questionnaires.

Figure 44: BDI scores at baseline

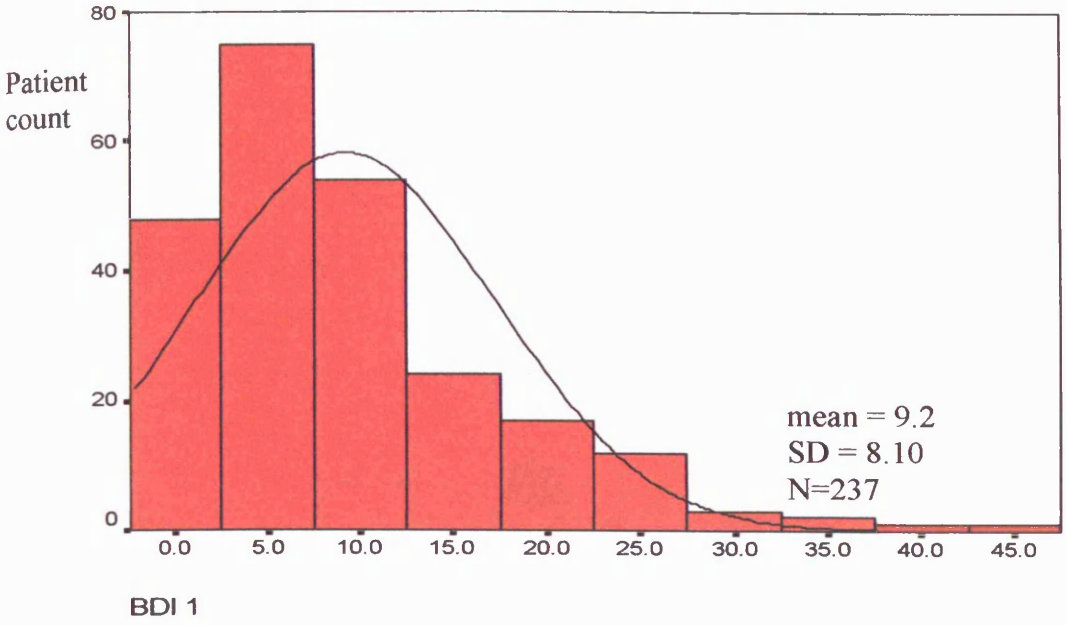


Figure 45: Amelioration in BDI scores at three months

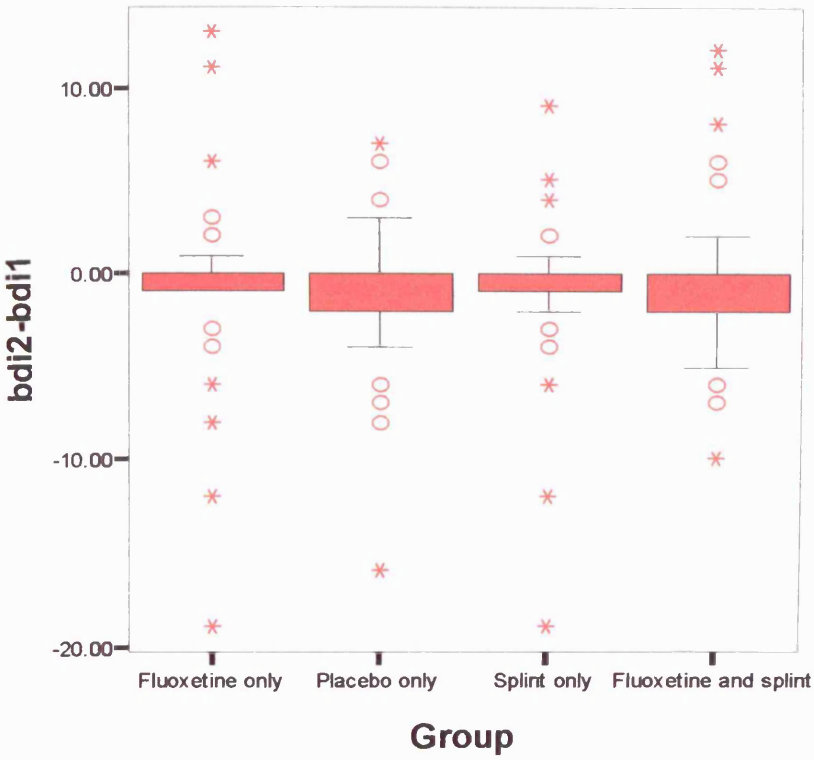


Figure 46: BDI levels

Not depressed (0-9), borderline (10-14), mild (15-20), severe (21 and above).

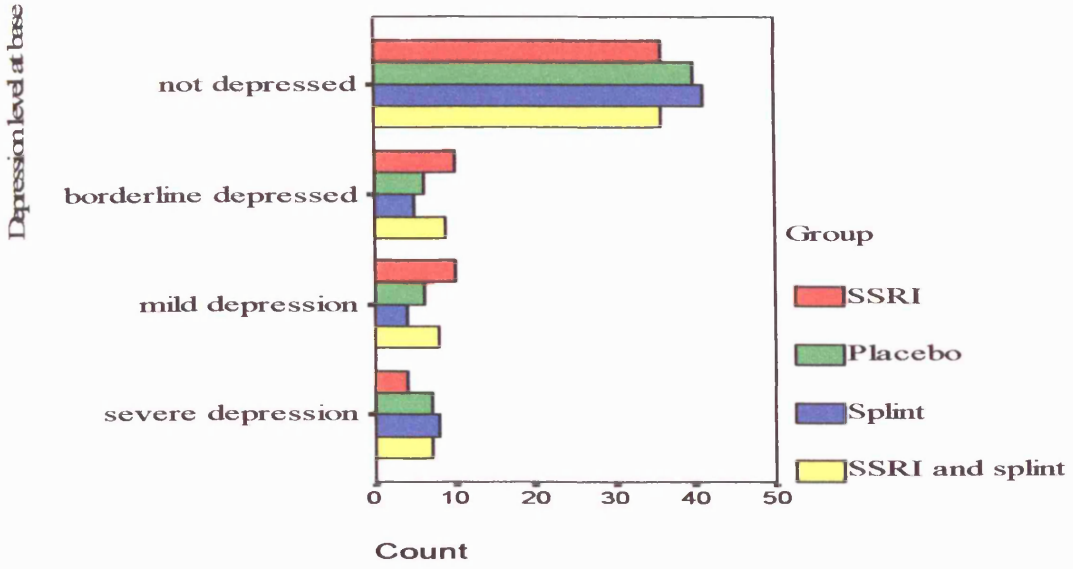
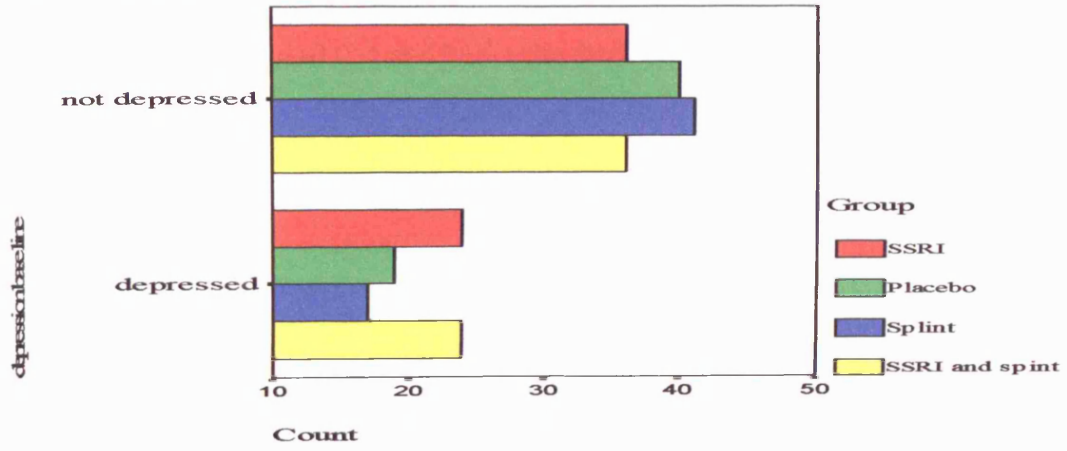


Table 35: Depression at baseline

Depression at baseline	SSRI	Placebo	Splint	SSRI and Splint	Total
No depression	36	40	41	36	153
Borderline	10	6	5	9	30
Mild	10	6	4	8	28
Severe	4	7	8	7	26
Total	60	59	58	60	237

Figure 47: BDI dichotomised into depressed and non depressed categories



8.1.4 Demographic details (Table 36)

Demographic details between depressed and non depressed categories were non significant apart from age, p=0.041.The depressed patients were slightly older with an average mean age of 34 (SD 10), compared to the non depressed who had an average age of 31 (SD 9).

8.1.5 Alteration in sleep patterns (Table 37, Figure 48)

There was a significant difference in reported sleep alteration. The depressed group suffering significantly increased sleep prevention and disturbance ($p<0.001$).

8.1.6 Emotional factors influencing pain (Table 36, Figure 49)

Emotional factors reported as an initiating factor for pain was just significantly raised in the depressed group (p=0.049). Emotional distress, identified by patients as a provoking factor for the pain, was significantly higher in the depressed group ($p<0.001$).

8.1.7 Recurrent chronic pains (Table 39)

Table 30, indicates there was a significant decrease in headaches (p=0.001), abdominal pain (p=0.001), neckache (p=0.01) and backache (p=0.01) in non depressed compared to depressed groups.

Logistic regression is then used to analyse these results in more detail and is presented with tables 40a and 40b.

Table 36: Demographic details for depressed and non-depressed groups (N=237)

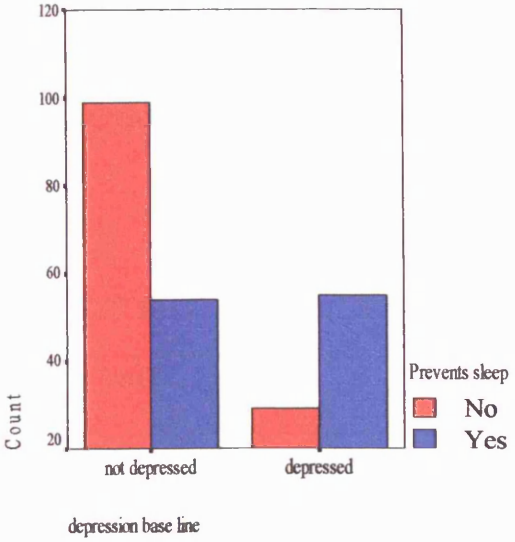
Recorded at baseline assessment	All groups (n=237)	**Depressed** (n=84)	**Nondepressed** (n=153)	Significance
Age (in years) Mean (+/- SD) Range	32.7 (16-55)	34.06 (10.08) (18-55)	31.37 (9.37) (16-53)	* (p=0.041)
Duration of pain (in yrs) Mean (+/- SD) Range	3.31(4.55) (0.25-32.0)	3.91 (5.73) (0.25-32.0)	2.98 (3.73) (0.25-22.00)	**ns** (p=0.131)
Gender M: F	54:183 22.8%:77.2%	18 : 66 21.4%: 78.6%	36 : 117 23.5%:76.5%	**ns** (p=0.712)
Referral source GDP GP Specialist	219 (92.4%) 5 (2.1%) 13 (5.5%)	75 (89.3%) 2 (2.4%) 7 (8.3%)	144 (94.1%) 3 (2.0%) 6 (3.9%)	**ns** (p=0.349)
Employment status Employed Unemployed Student Retired (medical) House wife	158 (66.7%) 18 (7.6%) 36 (15.2%) 1 (0.4%) 24 (10.1%)	62 (73.8%) 4 (4.8%) 12 (14.3%) 1 (1.2%) 5 (5.9%)	96 (62.7%) 14 (9.2%) 24 (15.7%) 0 (0%) 19 (12.4%)	**ns** (p=0.165)
Socio-economic status Professional I Intermmediate IIi Skilled non-manual IIii Skilled manual III Semi skilled IV Unskilled V Unemployed, house wife, student, retired VI	10 (4.2%) 75 (31.6%) 61 (25.7%) 8 (3.4%) 5 (3.3%) 1 (0.4%) 77 (32.5%)	4 (4.8%) 30 (35.7%) 24 (28.6%) 2 (2.4%) 1 (1.2%) 1 (1.2%) 22 (26.2%)	6 (3.9%) 45 (29.4%) 37 (24.2%) 6 (3.9%) 4 (2.6%) 0 (0%) 55 (36.0%)	**ns** (p=0.355)
Marital status Single Married Seperated Divorced Widowed	139(58.6%) 85 (35.9%) 2 (0.84%) 10 (4.2%) 1 (0.4%)	51 (60.7%) 30 (35.7%) 1 (1.2%) 2 (2.4%) 0 (0%)	88 (57.5%) 55 (35.9%) 1 (0.7%) 8 (5.2%) 1 (0.7%)	**ns** (p=0.702)

Significance test, Chi-squared (Independent samples t-test for age and duration) all **ns**.

Figure 48:

Sleep prevention and disturbance in depressed and non depressed groups

Sleep prevention (n=237)



Sleep disturbance (n=237)

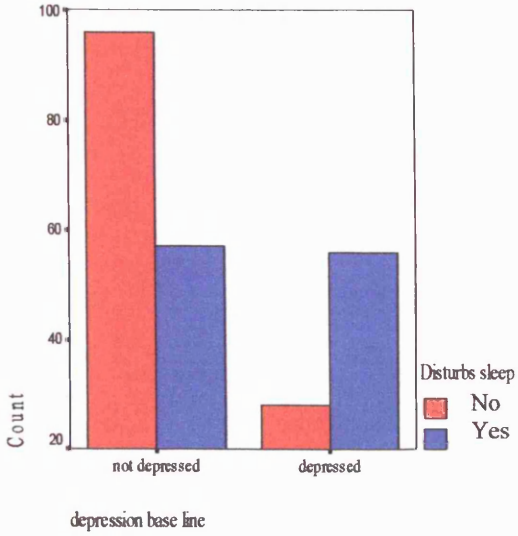


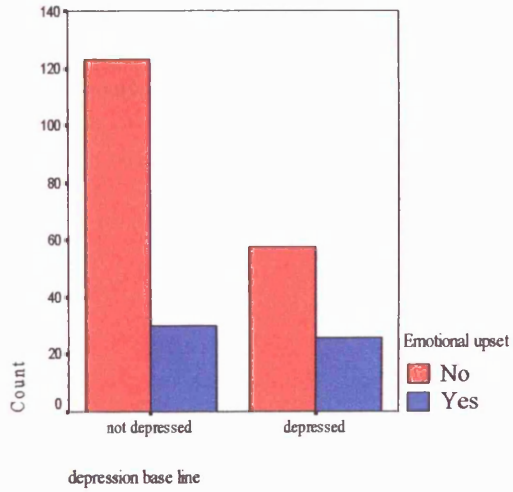
Table 37: Sleep alteration in depressed and non depressed groups

Sleep alteration	Non depressed (n=153)	Depressed (n=84)	Significance
Prevention	54 (35%)	55 (66%)	p<0.001
Disturbance	57 (37%)	56 (67%)	p<0.001

Figure 49:

Emotional factors influencing onset and provocation of pain

Emotional upset (initiating factor)



Emotional upset (provoking factor)

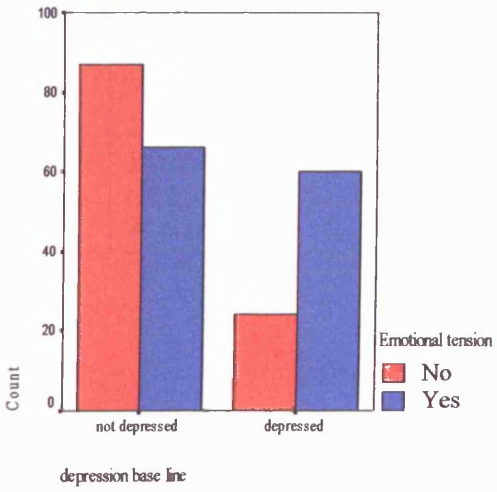


Table 38: Emotional distress in depressed and non depressed groups

Emotional distress	**Non depressed** (n=153)	**Depressed** (n=84)	Significance
Emotional upset (pain initiating factor)	30 (20%)	26 (31%)	p=0.049
Emotional upset (pain provoking factor)	66 (43%)	60 (71%)	p<0.001

Table 39:

Recurrent chronic pains for depressed and non depressed groups (n=237)

Chronic pains		**Non depressed** (n=153)	**Depressed** (n=84)	Significance (between groups)
Headache	Baseline	86 (56.2%)	60 (71.4%)	* p=0.021
	4 weeks	68 (44.4%)*	44 (52.4%)**	ns p=0.261
	8weeks	68 (44.4%)**	51 (60.7%)	* p=0.017
	12 weeks	58 (37.9%)***	51 (60.7%)	** p=0.001
		✸✸✸	✸✸	
Migraine	Baseline	43 (28.1%)	33 (39.3%)	ns p=0.078
	4 weeks	28 (18.3%)**	18 (21.4%)**	ns p=0.389
	8weeks	27 (17.6%)*	17 (20.2%)***	ns p=0.624
	12 weeks	23 (15.0%)***	19 (22.6%)**	ns p=0.143
		✸✸✸	✸✸✸	
Neckache	Baseline	65 (42.5%)	51 (60.7%)	* p=0.007
	4 weeks	43 (28.1%)**	40 (47.6%)*	ns p=0.119
	8weeks	52 (34.0%)*	36 (42.9%)**	ns p=0.176
	12 weeks	38 (24.8%)***	34 (40.5%)***	* p=0.012
		✸✸✸	✸✸✸	
Backache	Baseline	67 (43.8%)	48 (57.1%)	* p=0.049
	4 weeks	40 (26.1%)***	29 (34.5%)***	ns p=0.490
	8weeks	41 (26.8%)***	29 (34.5%)**	ns p=0.212
	12 weeks	37 (24.2%)***	31 (36.9%)***	* p=0.038
		✸✸✸	✸✸✸	
Abdominal pain	Baseline	36 (23.5%)	33 (39,3%)	* p=0.011
	4 weeks	16 (10.5%)***	18 (21.4%)*	ns p=0.512
	8weeks	18 (11.8%)***	18 (21.4%)	* p=0.047
	12 weeks	16 (10.5%)***	23 (27.4%)	**p=0.001
		✸✸✸	✸✸✸	

8.1.7.1 Logistic regression analysis of chronic pains in relation to depression

Table 40a:

Logistic regression analysis of chronic pains in relation to depression at baseline

Enter method	OR (Odds ratio)	95% CI (Confidence interval)	P value	Regression coefficient	SE (standard error)
Temporal (scalp) pain	2.67	1.45-4.93	0.002**	0.984	0.312
Abdominal pain	2.06	1.33-3.76	0.018*	0.725	0.306
Teeth pain	7.18	1.32-39.05	0.023*	1.97	0.864

* p<0.05, **p<0.005.

This model 69.6% correctly predicts depression at baseline, χ^2 =21.57 (3),p<0.001.

There is an almost 3 fold increase in likelihood of depression amongst those with reported temporal (scalp) muscle pain at baseline (OR=2.67,95% CI 1.45,4.93,p=0.002). There is a two fold increase amongst those with reported abdominal pain (OR=2.06,95%CI 1.33,3.76,p=0.018) and a remarkable seven fold increase in those with reported concomitant dental pain from clenching, bruxism or biting (OR=7.18 95%CI 1.32,39.05,p=0.023)

Analysing chronic pain report at three months again several factors predict depression.

Table 40b:

Logistic regression analysis of chronic pains in relation to depression at 3 months

Enter method	OR (Odds ratio)	95% CI (Confidence interval)	P value	Regression coefficient	SE (standard error)
Headache (3 months)	2.13	1.20-3.76	0.009*	0.76	0.38
Abdominal pain (3 months)	2.78	1.33-5.81	0.006*	1.02	0.56
Teeth pain (3 months)	3.49	1.18-10.40	0.024*	1.25	0.22

* p<0.05, **p<0.005

This model 71.3% correctly predicts depression at baseline, χ^2 =23.51 (3),p<0.001.

Headache at three months indicates a two fold increase in depression at baseline (OR=2.13,95%CI 1.20-3.76,p=0.009), abdominal pain nearly a three fold increase in likelihood of depression (OR=2.78,95%CI 1.33,5.81,p=0.006) and dental pain also a three fold increase (OR=3.49,95%CI 1.18,10.40,p=0.024).

8.1.8 Verbal reported pain rating scales

8.1.8.1 VAS (depressed and non depressed categories) (Table 41, figure 50)

8.1.8.1.1 Parametric analysis

Analysing the whole study cohort there is an observable and significant improvement in both depressed and non depressed categories at all three time points, $p<0.001$.
For individual groups, group1 significantly improved in both depressed and non depressed categories $p=0.001$ by three months. This improvement was not significantly perceptible at four weeks in the non depressed group, but both categories showed significant improvement during the eight and twelve week follow-up.
Interestingly, placebo group 2, showed no overall significant improvement amongst depressed subjects but significant improvement amongst the non depressed category $p<0.001$. With splint usage, group 3, again significant improvement was observed amongst the nondepressed subjects $p<0.001$ but to a lesser ,yet significant extent in the depressed category $p=0.003$. In group 4, again both depressed and nondepressed categories improved $p<0.005$ and $p<0.019$ respectively. Having observed the slight variation in pattern of improvement, there was nonetheless no significant differences in the improvement amongst depressed and non depressed categories between the four groups. Again, inter group analysis revealed no significant difference between groups.

8.1.8.1.2 Non parametric analysis

Analysing all groups together there was a significant improvement in both depressed and non depressed categories ($p<0.001$). Examining individual groups, this dual pattern was mirrored in group 4 combined therapy , depressed $p=0.001$ and non depressed $p=0.003$. Meanwhile, groups 1,2 and 3 only showed significant improvement in the non depressed groups ($p<0.001$) but less marked, although significant improvement in depressed categories for group 1 and 3 $p=0.004$ and $p=0.003$ respectively. However, group 2 placebo did not show overall improvement amongst the depressed individuals. Inter group analysis revealed no significant difference between groups.

8.1.8.2 PPI (depressed and non depressed categories) (Table 43)

Once again, analysing all groups synchronously there was a significant improvement in both the depressed and non depressed categories ($p<0.001$).

Intra group analysis did not reflect this pattern. Group 2 (placebo) showed no significant improvement over the three month course of therapy regardless of depression state. In group 4 (combined therapy) both depressed and non depressed groups reached the minimal level of significance $p=0.023$ and $p=0.006$ respectively. In group 3 (splint) the non depressed group significantly improved ($p=0.001$) with less marked, yet still significant improvement in the depressed category $p=0.024$.In group 1 (fluoxetine) the observation was reversed. It was the depressed group that significantly improved $p<0.001$ with no significant improvement in the non depressed category $p=0.066$.Overall, there was statistically no significant difference between groups.

8.1.8.3 Frequency (depressed and non depressed categories) (Table 44)

Improvement was observed in both depressed and non depressed categories. In combined groups for depressed and non depressed categories $p<0.001$. On closer inspection of the intra group analysis notably in groups 1,2 and 3 it was clearly the non depressed categories who exhibit the most significant improvement over the three time points,$p<0.001$, whilst the depressed categories are less significant $p=0.013$ (group1), $p=0.002$ (group2), $p=0.011$ (group3). In group 4 the depressed and non depressed categories both improved $p=0.003$ and $p=0.008$ respectively. Inter group analysis revealed no significant difference in improvement between the four groups.

8.1.8.4 Pain severity (depressed and non depressed categories) (Table 45)

A significant improvement was observed, amongst all groups together, in both depressed and non depressed categories, $p<0.001$. Analysing the intra group analysis it was clearly the non depressed categories who exhibit the most significant improvement over the three time points $p<0.001$. In groups 1,2 and 4 the improvement in depressed categories also reached significance, $p=0.006$ (group 1) $p=0.005$ (group 2) and $p=0.002$ (group 4). However, in group 3 the depressed category did not significantly improve $p=0.123$. Intergroup analysis was non significant.

8.1.8.5 Interference (depressed and non depressed categories) (Table 46)

Improvement was seen in both categories when analysisng all patients together $p<0.001$. This finding was also reflected in both groups 1 and 4 ($p<0.001$).However, only non depressed patients showed similar improvement ($p<0.001$) in groups 2 and 3. Depressed patients showed less significant improvement in group 2 ($p<0.005$) and group 3 ($p<0.05$).However, once again there was no inter group statistical significance.

Table 41: A comparison of Depressed / Non depressed categories - Imputation analysis (last score brought forward)

Pain response: **VAS (visual analogue scale)**,(10cm line) . A comparison of mean scores (+/- standard deviation)

Week	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=58)		Group 4 (n=60)		Significance between groups. One-way ANOVA	
	Depressed	Non depressed	Depressed	Non Depressed	Depressed	Non Depressed	Depressed	Non Depressed	Depressed	Non Depressed	Depressed	Non Depressed
0	6.15 (2.43)	5.60 (2.17)	6.60 (2.42)	5.62 (1.94)	5.33 (2.71)	6.25 (2.09)	5.89 (2.01)	5.40 (2.27)	6.54 (2.44)	5.11 (2.28)	**ns** p=0.286	**ns** p=0.126
4	4.97 (2.21) ***	4.62 (2.19) ***	5.01 (2.46) * p=0.008	4.67 (2.31) p=0.05	4.52 (2.21) p=0.274	5.14 (2.12) **p=0.004	5.41 (1.75) p=0.166	4.48 (2.08) * p=0.003	4.98 (2.30) ** p=0.003	4.18 (2.24) * p=0.022	**ns** p=0.702	**ns** p=0.275
8	4.70 (2.53) ***	4.21 (2.39) ***	4.93 (2.93) * p=0.015	4.34 (2.46) * p=0.014	4.29 (2.10) p=0.117	4.59 (2.42) ***	4.48 (1.81) * p=0.004	4.15 (2.46) **p=0.001	4.95 (2.91) * p=0.009	3.72 (2.23) ** p=0.004	**ns** p=0.791	**ns** p=0.447
12	4.31 (2.54) ***	3.90 (2.51) ***	4.17 (2.87) **p=0.001	3.64 (2.69) ** p=0.001	4.03 (2.04) * p=0.025	4.21 (2.52) ***	4.70 (2.10) * p=0.010	3.78 (2.42) ***	4.39 (2.91) * p=0.005	3.94 (2.50) * p=0.019	**ns** p=0.872	**ns** p=0.787
	✸✸✸	✸✸✸	✸✸ p=0.001	✸✸ p=0.001	ns p=0.11	✸✸✸	✸✸ p=0.003	✸✸✸	✸✸ p=0.005	✸ p=0.019		

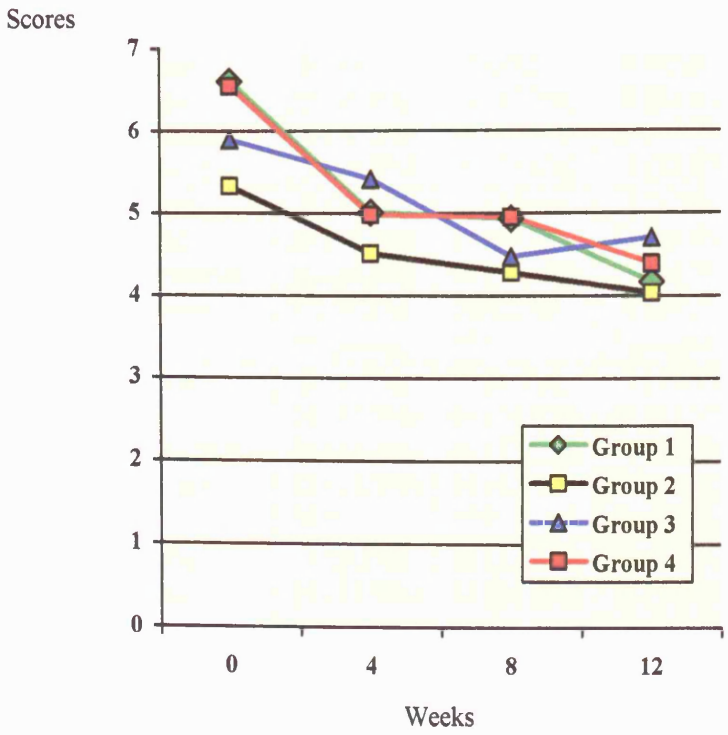
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Repeated measures ANOVA P<0.0001✸✸✸ P<0.005✸✸ P<0.05✸
Paired sample t-tests p<0.05 * p<0.005 ** p<0.001***

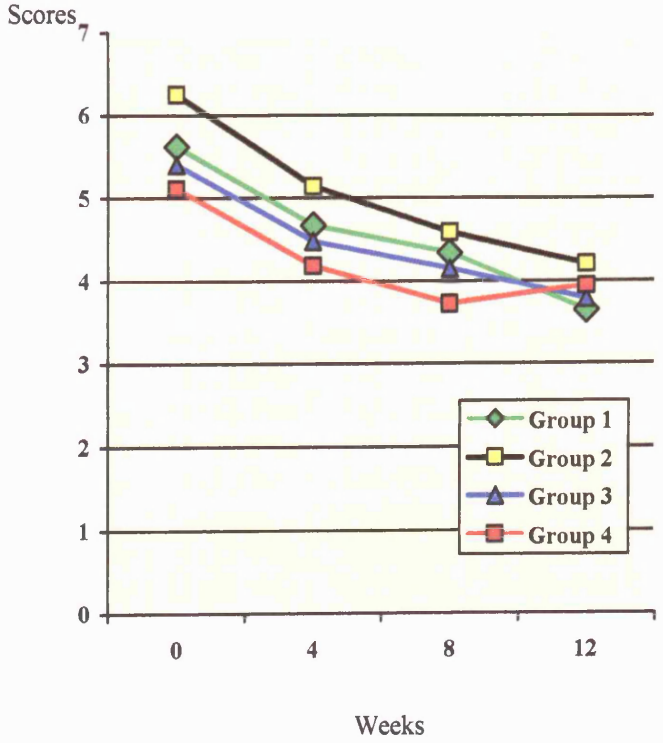
Inter group analysis : One –way ANOVA – not significant.

Figure 50 : VAS (visual analogue scale) A comparison of mean scores

Depressed (n=84)



Non depressed (n=153)



Group 1 – Fluoxetine medication
Group 2 – placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Table 42: Outcome measures – Present pain intensity scores - Depressed / Non Depressed - Intention needed to treat analysis

Week	Present pain intensity	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=58)		Group 4 (n=60)	
		Depressed (n=84)	Non Depressed (n=153)	Depressed (n=24)	Non Depressed (n=36)	Depressed (n=19)	Non Depressed (n=40)	Depressed (n=17)	Non Depressed (n=41)	Depressed (n=24)	Non Depressed (n=36)
0	None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Mild	25 (29.8%)	73 (47.7%)	6 (25.0%)	17 (47.2%)	6 (31.6%)	17 (42.5%)	6 (35.3%)	22 (53.7%)	7 (29.2%)	17 (47.2%)
	Moderate	34 (40.5%)	61 (39.9%)	10 (41.7%)	12 (33.3%)	9 (47.4%)	20 (50.0%)	6 (35.3%)	16 (39.0%)	9 (37.5%)	13 (36.1%)
	Severe	25 (29.8%)	19 (12.4%)	8 (33.3%)	7 (19.4%)	4 (21.1%)	3 (7.5%)	5 (29.4%)	3 (7.3%)	8 (33.3%)	6 (16.7%)
4	None	6 (7.1%)	9 (5.9%)	2 (8.3%)	2 (5.6%)	3 (15.8%)	1 (2.5%)	1 (5.9%)	4 (9.8%)	0 (0%)	2 (5.6%)
	Mild	30 (35.7%)	84 (54.9%)	11 (45.8%)	19 (52.8%)	4 (21.1%)	20 (50.0%)	6 (35.3%)	27 (65.9%)	9 (37.5%)	18 (75.0%)
	Moderate	31 (36.9%)	46 (30.1%)	4 (16.7%)	8 (22.2%)	10 (52.6%)	16 (40.0%)	7 (41.2%)	8 (19.5%)	10 (24.4%)	14 (38.9%)
	Severe	17(20.2%)	14(9.2%)	7 (29.2%)	7 (19.4%)	2 (10.5%)	3 (7.5%)	3 (17.6%)	2(4.9%)	5 (20.8%)	2 (5.6%)
		** (p=0.002)	***	* (p=0.020)	ns (p=0.186)	ns (p=0.141)	ns (p=0.251)	ns (p=0.317)	** (p=0.001)	ns (p=0.212)	ns (p=0.079)
8	None	8 (9.5%)	13 (8.5%)	3 (12.5%)	2 (5.6%)	3 (15.8%)	4 (10.0%)	1 (5.9%)	3 (7.3%)	1 (4.2%)	4 (11.1%)
	Mild	36 (42.9%)	84 (54.9%)	10 (41.7%)	19 (52.8%)	6 (31.6%)	19 (47.5%)	7 (41.2%)	26 (63.4%)	13 (54.2%)	20 (55.6%)
	Moderate	28 (33.3%)	42 (27.5%)	6 (25.0%)	10 (27.8%)	8 (42.1%)	14 (35.0%)	8 (47.1%)	9 (22.0%)	6 (25.0%)	9 (25.0%)
	Severe	12 (14.3%)	14 (9.2%)	5 (20.8%)	5 (13.9%)	2 (10.5%)	3 (7.5%)	1 (5.9%)	3 (7.3%)	4 (16.7%)	3 (8.3%)
		***	***	* (p=0.012)	ns (p=0.059)	* (p=0.070)	* (p=0.032)	ns (p=0.083)	ns (p=0.072)	* (p=0.020)	* (p=0.016)
12	None	8 (9.5%)	20 (13.1%)	2 (8.3%)	2 (5.6%)	2 (10.5%)	7 (17.5%)	2 (11.8%)	6 (14.6%)	2 (8.3%)	5 (13.9%)
	Mild	35 (41.7%)	81 (52.9%)	12 (50.0%)	22 (61.1%)	7 (36.8%)	15 (37.5%)	9 (53.0%)	26 (63.4%)	7 (29.2%)	18 (50.0%)
		30 (35.7%)	39 (25.5%)	7 (29.2%)	7 (19.4%)	9 (47.4%)	16 (40.0%)	3 (17.6%)	6 (14.6%)	11 (45.8%)	10 (27.8%)
	Moderate	11 (13.1%)	13 (8.5%)	3 (12.5%)	5 (13.9%)	1 (5.3%)	2 (5.0%)	3 (17.6%)	3 (7.3%)	4 (16.7%)	3 (8.3%)
	Severe	***	***	* (p=0.017)	* (p=0.006)	* (p=0.046)	* (p=0.026)	* (p=0.007)	* (p=0.006)	ns (p=0.070)	** (p=0.003)
		✱✱✱	✱✱✱	✱✱✱	ns (p=0.066)	ns (p=0.187)	ns (p=0.099)	✱p=0.024	✱✱(p=0.001)	✱p=0.023	✱p=0.006

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001✱✱✱
Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***

Inter group anaysis : Kruskall -Wallis (not significant)

Table 43: Outcome measures – Frequency scores - Depressed / Non Depressed - Intention needed to treat analysis

Week	Frequency scores	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=58)		Group 4 (n=60)	
		Depressed (n=84)	Non Depressed (n=153)	Depressed (n=24)	Non Depressed (n=36)	Depressed (n=19)	Non Depressed (n=36)	Depressed (n=17)	Non Depressed (n=41)	Depressed (n=24)	Non Depressed (n=36)
0	Never	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Occasional	5 (6%)	11 (7.2%)	0 (0%)	0 (0%)	1 (5.3%)	2 (5.6%)	1 (5.9%)	5 (12.2%)	3 (12.5%)	4 (11.1%)
	Often	28 (33.3%)	50 (32.7%)	9 (37.5%)	12 (33.3%)	8 (42.1%)	11 (30.6%)	6 (35.3%)	15 (36.6%)	5 (20.8%)	12 (33.3%)
	Always	51 (60.7%)	92 (60.1%)	15 (62.5%)	24 (66.7%)	10 (52.6%)	27 (75.0%)	10 (58.8%)	21 (51.2%)	16 (66.7%)	20 (55.6%)
4	Never	3 (3.6%)	2 (1.3%)	0 (0%)	0 (0%)	2 (10.5%)	1 (2.8%)	1 (5.9%)	1 (2.4%)	0 (0%)	0 (0%)
	Occasional	19 (22.6%)	46 (30.1%)	6 (25.0%)	11 (30.6%)	2 (10.5%)	9 (25.0%)	2 (11.8%)	14 (34.1%)	9 (37.5%)	12 (33.3%)
	Often	29 (34.5%)	51 (33.3%)	5 (20.8%)	11 (30.6%)	9 (47.4%)	14 (38.9%)	9 (52.9%)	15 (36.6%)	6 (25.0%)	11 (30.6%)
	Always	33 (39.3%)	54 (35.3%)	13 (54.2%)	14 (38.9%)	6 (31.6%)	16 (44.4%)	5 (29.4%)	11(26.8%)	9 (37.5%)	13 (36.1%)
		***	***	ns (p=0.074)	***	* (p=0.030)	** (p=0.004)	* (p=0.023)	** (p=0.004)	* (p=0.010)	* (p=0.031)
8	Never	4 (4.8%)	12 (7.8%)	1 (4.2%)	2 (5.6%)	2 (10.5%)	2 (5.6%)	0 (0%)	4 (9.8%)	1 (4.2%)	4 (11.1%)
	Occasional	22 (26.2%)	42 (27.5%)	8 (33.3%)	10 (27.8%)	2 (10.5%)	10 (27.8%)	3 (17.6%)	15 (36.6%)	9 (37.5%)	7 (19.4%)
	Often	30 (35.7%)	50 (32.7%)	4 (16.7%)	8 (22.2%)	9 (25.0%)	15 (41.7%)	11 (64.7%)	14 (34.1%)	6 (25.0%)	13 (36.1%)
	Always	28 (33.3%)	49 (32%)	11(45.8%)	16 (44.4%)	6 (31.6%)	13 (36.1%)	3 (17.6%)	8 (19.5%)	8 (33.3%)	12 (33.3%)
		***	***	* (p=0.008)	** (p=0.001)	* (p=0.030)	***	* (p=0.007)	***	** (p=0.004)	* (p=0.007)
12	Never	8 (9.5%)	18 (11.8%)	2 (8.3%)	3 (8.3%)	2 (10.5%)	6 (16.7%)	1 (5.9%)	4 (9.8%)	3 (12.5%)	5 (13.9%)
	Occasional	14 (16.7%)	44 (28.8%)	6 (25.0%)	9 (25.0%)	3 (15.8%)	10 (27.8%)	1 (5.9%)	20 (48.8%)	4 (16.7%)	5 (13.9%)
	Often	31 (36.9%)	43 (28.1%)	5 (20.8%)	11 (30.6%)	9 (47.4%)	13 (36.1%)	9 (52.9%)	10 (24.4%)	8 (33.3%)	9 (25.0%)
	Always	31 (36.9%)	48 (31.4%)	11 (45.8%)	13 (36.1%)	5 (26.3%)	11 (30.6%)	6 (35.3%)	7 (17.1%)	9 (37.5%)	17 (47.2%)
		***	***	* (p=0.014)	***	* (p=0.015)	***	ns (p=0.096)	***	* (p=0.012)	ns (p=0.053)
		***	***	*(p=0.013)	***	**(p=0.002)	***	*(p=0.011)	***	**(p=0.003)	*(p=0.008)

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001***
Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***

Inter group anaysis : Kruskall -Wallis (not significant)

Table 44: Primary outcome measure – Pain response Depressed / Non Depressed - Intention needed to treat analysis

Week	Severity	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=58)		Group 4 (n=60)	
		Depressed (n=84)	Non Depressed (n=153)	Depressed (n=24)	Non Depressed (n=36)	Depressed (n=19)	Non Depressed (n=40)	Depressed (n=17)	Non Depressed (n=41)	Depressed (n=24)	Non Depressed (n=36)
4	Worse	5 (6%)	11 (7.2%)	2 (8.3%)	2 (5.6%)	0 (0%)	2 (5.0%)	1 (5.9%)	3 (7.3%)	2 (8.3%)	4 (11.1%)
	In pain	48(57.1%)	86 (56.2%)	13 (54.2%)	17(47.2%)	13 (68.4%)	26 (65.0%)	13 (76.5%)	22 (53.7%)	9 (37.5%)	21(58.3%)
	Improved	28 (33.3%)	53 (34.6%)	8 (33.3%)	16 (44.4%)	4 (21.1%)	11 (27.5%)	3 (17.6%)	15 (36.6%)	13 (54.2%)	11 (30.6%)
	Pain free	3(3.6%)	3 (2%)	1 (4.2%)	1 (2.8%)	2 (10.5%)	1(2.5%)	0 (0%)	1 (2.4%)	0 (0%)	0 (0%)
		***	***	* (p=0.033)	** (p=0.001)	* (p=0.023)	* (p=0.008)	ns (p=0.317)	** (p=0.003)	* (p=0.005)	ns (p=0.071)
8	Worse	6 (7.1%)	5 (3.3%)	2 (8.3%)	1 (2.8%)	0 (0%)	1 (2.5%)	3 (17.6%)	2 (4.9%)	1 (4.2%)	1 (2.8%)
	In pain	39 (46.4%)	80 (52.3%)	11 (45.8%)	22 (61.1%)	12 (63.2%)	19 (47.5%)	6 (35.3%)	21 (51.2%)	10 (41.7%)	18 (50.0%)
	Improved	34 (40.5%)	57 (37.3%)	10 (41.7%)	11 (30.6%)	4 (21.1%)	17 (42.5%)	8 (47.1%)	15 (36.6%)	12 (50.0%)	14 (38.9%)
	Pain free	5 (6%)	11(7.2%)	1(4.2%)	2(5.6%)	3(15.8%)	3 (7.5%)	0 (0%)	3 (7.3%)	1(4.2%)	3 (8.3%)
		***	***	* (p=0.012)	** (p=0.002)	* (p=0.015)	***	ns (p=0.132)	***	** (p=0.002)	***
12	Worse	7 (8.3%)	8 (5.2%)	2 (8.3%)	2 (5.6%)	0 (0%)	1 (2.5%)	2 (11.8%)	2 (4.9%)	3 (12.5%)	3 (8.3%)
	In pain	41 (48.8%)	71(46.4%)	10 (41.7%)	17 (47.2%)	13 (68.4%)	20 (50.0%)	7 (41.2%)	18 (43.9%)	11 (45.8%)	16 (44.4%)
	Improved	28 (33.3%)	54 (35.3%)	10 (41.7%)	13 (36.1%)	4 (21.1%)	12 (30.0%)	7 (41.2%)	17 (41.5%)	7 (29.2%)	12 (33.3%)
	Pain free	8 (9.5%)	20 (13.1%)	2 (8.3%)	4 (11.1%)	2 (10.5%)	7(17.5%)	1 (5.9%)	4 (9.8%)	3 (12.5%)	5 (13.9%)
		***	***	* (p=0.007)	** (p=0.001)	* (p=0.023)	***	ns (p=0.052)	***	* (p=0.032)	** (p=0.001)
		***	***	* (p=0.006)	***	* (p=0.005)	***	ns (p=0.123)	***	** (p=0.002)	***

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001***
Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***

Inter group anaysis : Kruskall -Wallis (not significant)

Table 45: Primary outcome measure – Depressed / Non depressed groups - Interference with life (Intention to treat analysis)

Week	Interference	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=60)		Group 4 (n=60)	
		Depressed (n=84)	Non Depressed (n=153)	Depressed (n=24)	Non Depressed (n=36)	Depressed (n=19)	Non Depressed (n=40)	Depressed (n=17)	Non Depressed (n=41)	Depressed (n=24)	Non depressed (n=36)
0	Yes	84(100%)	153(100%)	24(100%)	36 (100%)	19(100%)	40 (100%)	17 (100%)	41(100%)	24(100%)	36(100%)
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4	Yes	51(60.7%)	85 (55.6%)	14(58.3%)	16 (44.4%)	14(73.7%)	25(62.5%)	10 (58.8%)	19(46.3%)	13(54.2%)	25(69.4%)
	No	33(39.3%) ***	68(44.4%) ***	10(41.7%) ** (p=0.002)	20(55.6%) ***	5 (26.3%) ns (p=0.063)	15(37.5%) ***	7 (41.2%) * (p=0.016)	22(53.7%) ***	11(45.8%) ** (p=0.001)	11(30.6%) ** (p=0.001)
8	Yes	46(54.8%)	75 (49%)	12 (50.0%)	17 (47.2%)	12(63.2%)	20(50.0%)	11 (64.7%)	20(48.8%)	11(45.8%)	18 (50%)
	No	38(45.2%) ***	78(51%) ***	12(50.0%) ** (p=0.001)	19(52.8%) ***	7(36.8%) * (p=0.016)	20(50.0%) ***	6 (35.3%) * (p=0.031)	21(51.2%) ***	13(54.2%) ***	18 (50%) ***
12	Yes	48(57.1%)	66 (43.1%)	13 (54.2%)	15 (41.7%)	11(57.9%)	19(47.5%)	10(58.8%)	18(43.9%)	14 (58.3%)	14(38.9%)
	No	36(42.9%) ***	87(56.9%) ***	11(45.8%) ***	21(58.3%) ***	8 (42.1%) * (p=0.008)	21(52.5%) ***	7 (41.2%) * (p=0.016)	23(56.1%) ***	10 (41.7%) ** (p=0.002)	22(61.1%) ***
		***	***	***	***	** (p=0.002)	***	** (p=0.004)	***	***	***

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Cochran Test P<0.001 ***
McNemar Test P<0.001 ***
Chi squared not significant between groups

8.1.9 Self-report pain questionnaires outcome measures in depression

8.1.9.1 MPI (Depressed and non depressed categories) (Table 47, figure 51)

Analysing all groups together, the patient's perspective of pain improved, during the three months treatment phase, in severity, interference and affective distress amongst both depressed and non depressed categories. MPI severity improved significantly regardless of depression $p<0.001$. Similarly, MPI interference: depressed $p<0.001$, non depressed $p=0.001$, MPI affective distress: depressed $p=0.001$ and to a lesser extent in the non depressed $p=0.003$.

In group 1 the depressed category appeared to improve most significantly. MPI severity $p=0.010$, interference $p=0.004$, life control $p=0.015$ and affective distress $p=0.023$, whilst only interference improved in the non depressed $p=0.030$. Conversely, in group 3, the non depressed category appeared to improve most significantly; MPI severity $p=0.008$, interference $p=0.002$ in the non depressed. Only severity in the depressed significantly improved $p=0.027$. Severity, interference and affective distress improved in depressed and non depressed cateogories of group 2 but not life control. MPI life control only appeared to have improved amongst groups 1 and 4 with depression $p=0.015$ and $p=0.04$ respectively. As an incidental finding the MPI level of support from others appeared to decrease in the non depressed group 3, $p=0.010$. Once again all these apparent variations between groups were not substantiated by rigorous inter group analysis.

8.1.9.2 MPQ (Depressed and non depressed categories) (Table 48, Figure 52)

Together, the groups showed significant improvement amongst both the depressed and non depressed categories, PPI ($p<0.001$) and MPQ sensory % ($p<0.005$). In non

depressed categories VAS and MPQ total % were significantly reduced $p<0.001$.This was reflected to a lesser extent in the depressed category VAS $p<0.05$ and MPQ total% $p<0.005$. MPQ affective % showed significant improvement in the depressed category $p<0.05$.

Within groups analysis was variable. A significant improvement in PPI was noted amongst depressed categories in groups 1 and 2 ($p<0.05$) but conversely non depressed categories in groups 3 and 4 ($p<0.05$). Only non depressed patients appeared to improve significantly in group 3, PPI $p<0.05$, MPQ: sensory % $p<0.05$ and affective % $p<0.05$ and total % $p<0.005$. Inter group analysis revealed no significant difference.

8.1.9.3 BDI (Depressed and non depressed categories)

Composite scores decreased significantly in the depressed category in all groups $p<0.005$. This was reiterated in group 1, $p<0.05$ and group 2 ,$p<0.005$, yet statistically there was no significant difference between groups.

8.1.9.4 Kellner (Depressed and non depressed categories)

Hypochondriacal beliefs reduced in the non depressed category in the analysis of all groups $p<0.05$. Intra and inter group analysis revealed no significant differences.

8. 1.9.5 Logistic regression analysis of questionnaire scores in depression

Following the earlier bivariate correlations for the self report pain questionnaires, a logistic regression analysis was also performed for pain rating scores as predictors of depression. Only a small number of variables remained as significant predictors.

Table 46: Logistic regression analysis of questionnaire scores in depression

Enter method	OR (Odds ratio)	95% CI (Confidence interval)	P value	Regression coefficient	SE (standard error)
MPI (life control)	0.45	0.30-0.67	<0.001 ***	-0.81	0.21
MPI (punishing response)	1.50	1.10-2.04	0.010 *	0.41	0.16
MPI (activities away from home)	0.68	0.47-1.00	0.047 *	-0.38	0.19
MPQ (sensory)	1.02	1.00-1.04	0.063	0.02	0.01
Kellner (total)	1.24	1.12-1.38	<0.001 ***	0.22	0.05

* $p<0.05$, **$p<0.005$,***$p<0.001$

The model 82.4% correctly predicts depression at baseline, $\chi^2 = 79.55$ (5),$p<0.001$.

As expected, decrease in MPI (life control) score indicates an increase in depression, (OR=0.45,95% CI 0.30,0.67,$p<0.001$) whilst an increase in Kellner illness attitude (hypochondriacal beliefs and disease phobia) indicates an increased prediction of depression,(OR=1.24,95%CI 1.12,1.38,$p<0.001$).An increase in MPI (punishing response of others) increases the chances of depression(OR=1.50,95% CI 1.10,2.04,$p<0.01$) whilst an increased score of MPI (activities away from home) decreases the chances of depression (OR=0.68,95% CI 0.47,1.00,$p=0.047$).

Table 47: Multidimensional pain inventory (MPI) A comparison of median scores (25^{th},75^{th} percentiles) between the start and finish of the three months. (Depressed and Non depressed groups)

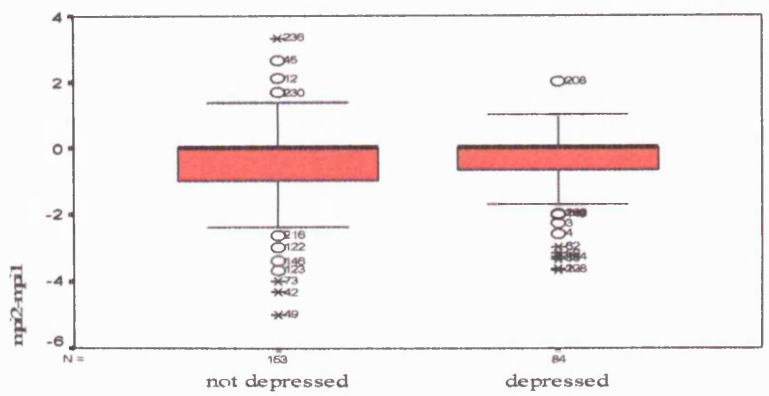
MPI	Study	All groups		Group 1		Group 2		Group 3		Group 4	
		Depressed	Non depressed	Depressed	Non depressed	Depressed	Non depressed	Depressed	Non Depressed	Depressed	Non Depressed
Patients perspective of pain											
MPI - Severity	Start	3.47 (2.60,4.65)	2.66 (1.66,3.66)	3.60 (2.15,4.32)	3.17 (2.00,4.25)	3.00 (2.60,4.00)	3.15 (2.33,4.00)	3.00 (2.47,4.48)	2.33 (1.30,3.00)	4.00 (2.57,5.00)	2.17 (1.30-3.00)
	Finish	2.66 (1.60,4.00) ***	2.00 (1.30,3.33) ***	2.67 (1.04,4.00) *(p=0.010)	2.60 (1.62,4.00)	2.60 (1.60,3.00) * (p=0.012)	2.33 (1.08,3.92) **(p=0.002)	3.00 (2.17,4.30) * (p=0.027)	1.60 (0.66,2.66) * (p=0.008)	4.00 (2.00,5.00)	2.00 (1.30,3.00)
MPI - Interference	Start	2.77 (1.29,4.10)	1.14 (0.46,1.90)	2.90 (1.29,3.90)	1.39 (0.62,2.53)	1.91 (0.82,3.54)	1.45 (0.68,2.27)	2.30 (1.85,4.37)	0.95 (0.41,1.55)	3.19 (1.26,4.25)	0.77 (0.28,1.30)
	Finish	2.33 (0.90,3.72) ***	0.73 (0.30,1.73) **(p=0.001)	2.54 (0.33,3.58) **(p=0.004)	0.86 (0.32,2.00) * (p=0.030)	1.16 (0.73,3.36) *(p=0.008)	1.09 (0.47,2.20) *(p=0.030)	2.50 (2.14,4.27)	0.54 (0.23,1.41) **(p=0.002)	2.50 (1.00,4.16)	0.59 (0.26,1.30)
MPI – Life control	Start	2.38 (1.50,3.25)	3.75 (3.00,4.25)	2.38 (1.06,2.94)	3.71 (3.00,4.25)	2.25 (1.25,3.25)	3.75 (2.75,4.50)	2.25 (2.13,3.25)	3.50 (2.75,4.13)	2.63 (2.00,3.44)	3.75 (3.06,4.50)
	Finish	2.75 (1.81.3.75) **(p=0.002)	3.75 (3.00,4.50) *(p=0.066)	2.88 (2.00,3.94) *(p=0.015)	3.75 (3.25,4.50)	2.75 (1.50,3.75)	3.75 (3.06,4.50)	2.50 (2.00,3.38)	3.60 (2.75,4.25)	2.75 (1.75,4.19) * (p=0.040)	3.75 (3.0,4.25)
MPI – Affective distress	Start	4.00 (3.33,4.92)	3.00 (2.00,3.66)	4.00 (3.08,5.00)	3.30 (2.40,3.92)	4.00 (3.60,5.33)	3.00 (2.00,4.00)	3.66 (3.15,4.47)	2.60 (1.66,3.47)	4.00 (2.83,4.83)	2.66 (2.0,3.65)
	Finish	3.66 (3.00,4.33) **(p=0.001)	2.66 (1.60,3.63) **(p=0.003)	3.50 (2.60,4.23) *(p=0.023)	3.00 (1.33,3.92) ns (p=0.053)	3.66 (3.33,5.30) *(p=0.028)	2.66 (1.33,3.58) *(p=0.041)	3.66 (2.83,4.32)	2.66 (1.63,3.66)	3.33 (2.70,4.58)	2.33 (1.66,3.0)
Response of significant other											
MPI – Support response	Start	3.00 (1.83,4.47)	3.60 (2.60,4.66)	3.25 (1.32,5.08)	3.60 (2.47,4.66)	2.60 (0.9,4.75)	4.00 (3.00,5.00)	3.15 (2.41,4.33)	3.17 (2.40,4.66)	3.00 (1.83,4.33)	3.30 (2.6,4.47)
	Finish	3.42 (1.92,4.33)	3.33 (2.33,4.66)	3.42 (1.00,4.75)	3.47 (2.53,4.33)	2.80 (0.9,4.62)	4.00 (3.00,5.30)	3.30 (2.33,4.00)	3.00 (1.60,4.33) * (p=0.010)	3.66 (2.00,4.47)	3.47 (2.53,4.62)
MPI Punishing response	Start	1.50 (0.50,2.75)	0.66 (0.00,1.50)	1.13 (0.31,2.94)	0.71 (0.63,1.75)	2.00 (1.00,3.75)	1.00 (0,2.00)	1.38 (0.50,2.94)	0.50 (0,1.94)	1.75 (0.63,2.31)	0.50 (0,1.0)
	Finish	1.75 (0.94,3.00)	0.50 (0,1.25)	1.38 (0.75,2.81)	0.75 (0,2.00)	1.75 (1.25,2.75)	0.63 (0,2.13)	1.38 (1.00,2.81)	0.50 (0,1.81)	2.25 (0.75,3.00)	0.38 (0,1.0)

MPI	Study	All groups		Group 1		Group 2		Group3		Group 4	
		Depressed	Non depressed	Depressed	Non depressed	Depressed	Non depressed	Depressed	Non Depressed	Depressed	Non Depressed
MPI Solicitous response	Start	2.66 (1.30,3.67)	2.66 (1.50,4.00)	3.23 (2.20,4.45)	2.13 (1.30,3.46)	2.66 (1.72,3.25)	2.83 (1.71,4.53)	2.58 (1.13,3.91)	2.66 (1.53,3.83)	1.80 (0.66,3.75)	3.0 (1.72,4.16)
	Finish	2.63 (1.00,3.83)	2.60 (1.33,4.00)	3.08 (1.43,4.42)	2.00 (1.16,3.42)	2.50 (1.33,3.25)	2.92 (1.29,4.53)	2.63 (1.13,3.88)	2.63 (1.50,4.37)	2.83 (0.92,3.50)	2.50 (1.48,3.58)
MPI Distracting response	Start	1.75 (0.63,3.00)	1.75 (0.75,2.75)	2.00 (0.75,2.88)	1.88 (0.81,2.50)	1.50 (0.38,2.63)	1.63 (0.94,3.25)	2.38 (0.56,2.94)	1.63 (0.56,2.75)	1.63 (0.56,3.00)	1.75 (0.25,2.88
	Finish	2.00 (0.75,3.00)	1.50 (0.75,2.75)	2.38 (0.75,3.38)	1.50 (0.88,2.38)	1.25 (0.63,1.88)	1.63 (0.69,3.00)	2.38 (0.88,3.19)	1.63 (0.44,2.75)	2.00 (1.13,3.00)	1.63 (0.19,3.0)
Frequency of participation											
MPI – Household chores	Start	5.00 (3.65,5.60)	4.80 (3.55,5.60)	5.00 (3.60,5.75)	4.70 (3.30,5.55)	4.00 (3.40,5.20)	5.20 (3.25,5.95)	5.20 (3.40,5.90)	4.50 (3.50,5.40)	5.00 (3.90,5.75)	4.80 (3.85,5.20)
	Finish	5.00 (3.80,5.60)	4.40 (3.60,5.60)	4.70 (4.20,5.75)	4.60 (3.70,5.24)	4.60 (3.40,5.20)	4.40 (3.60,5.80)	5.00 (3.80,5.70)	4.40 (3.60,5.40)	5.20 (3.85,5.60)	4.40 (3.25,5,51)
MPI – Outdoor work	Start	2.00 (0.95,3.00)	2.00 (1.10,3.00)	2.00 (1.43,2.94)	1.75 (1.20,2.75)	2.45 (1.20,3.55)	1.78 (0.73,3.05)	2.00 (0.90,3.13)	2.00 (1.00,2.60)	1.40 (0.68,3.00)	2.00 (1.2,3.28)
	Finish	2.20 (1.00,3.60)	1.75 (1.00,2.60)	2.35 (1.38,3.35)	1.50 (1.00,2.50)	2.28 (1.20,3.90)	1.90 (0.94,2.70)	1.90 (0.79,3.20)	1.90 (1.00,2.60)	1.60 (0.80,3.20)	2.10 (1.0,3.05)
MPI – Activities away from home	Start	3.00 (2.25,4.00)	3.75 (3.25,4.50)	3.13 (2.50,4.19)	3.75 (2.81,4.63)	3.50 (2.25,4.25)	4.00 (3.00,4.50)	2.25 (1.63,3.88)	3.50 (3.25,4.25)	3.13 (2.06,3.94)	4.00 (3.25,4.94)
	Finish	3.00 (2.25,4.00)	3.75 (3.00,4.50)	3.13 (2.31,3.94)	3.75 (3.00,4.25)	3.50 (2.50,4.25)	3.75 (3.00,4.50)	2.75 (1.75,4.0)	3.75 (3.25,4.50)	3.00 (2.50,3.88)	3.75 (2.81,4.75
MPI – Social activities	Start	2.75 (2.00,3.75)	3.25 (2.50,4.00)	2.50 (2.0,3.63)	3.00 (2.50,4.25)	2.75 (2.30,4.00)	3.50 (2.50,4.00)	3.00 (1.75,3.63)	3.00 (2.50,3.75)	3.13 (2.00,4.13)	3.50 (2.31,4.19)
	Finish	3.00 (2.00,3.75)	3.42 (2.58,4.00)	2.63 (2.00,3.90)	3.25 (2.33,4.00)	3.00 (2.33,4.00)	3.58 (2.81,4.00)	3.00 (2.00,3.75)	3.25 (2.50,3.75)	3.13 (1.56,3.69)	3.50 (2.75,4.19)
MPI – General activity level	Start	3.30 (2.71,3.74)	3.49 (2.81,4.02)	3.36 (2.76,3.73)	3.50 (2.83,2.97)	3.23 (2.68,3.81)	3.54 (2.82,4.01)	3.39 (2.16,3.90)	3.33 (2.77,3.76)	3.24 (2.78,3.63)	3.57 (2.82,4.10)
	Finish	3.26 (2.69,3.75)	3.36 (2.90,3.88)	3.31 (2.59,3.76)	3.48 (2.78,3.91)	3.11 (2.88,3.99)	3.42 (2.86,3.98)	3.39 (2.38,3.79)	3.30 (2.96,3.64)	3.21 (2.78,3.57)	3.30 (3.03,3.90

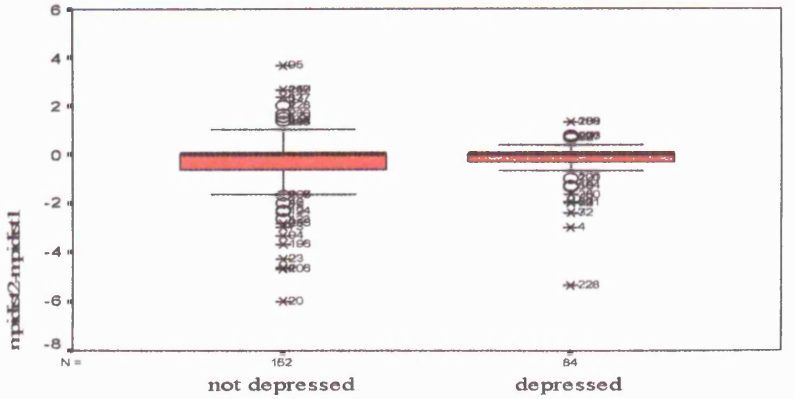
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p< 0.001$
Kruskall Wallice not significant between groups

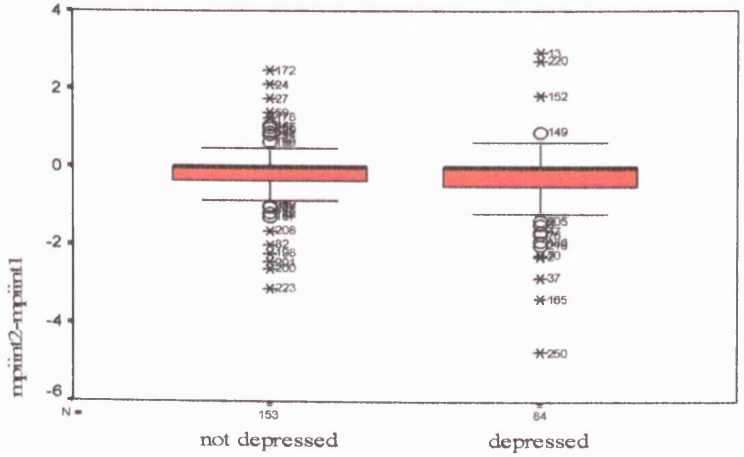
Figure 51: Change in MPI scores over three months (Depressed / Non depressed



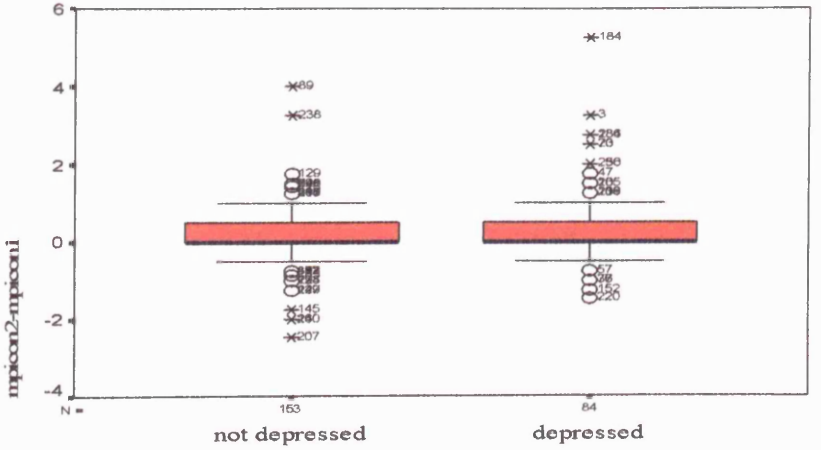
Change in MPI-severity at three months



Change in MPi-affective distress at 3 months



Change in MPI-interference at three months



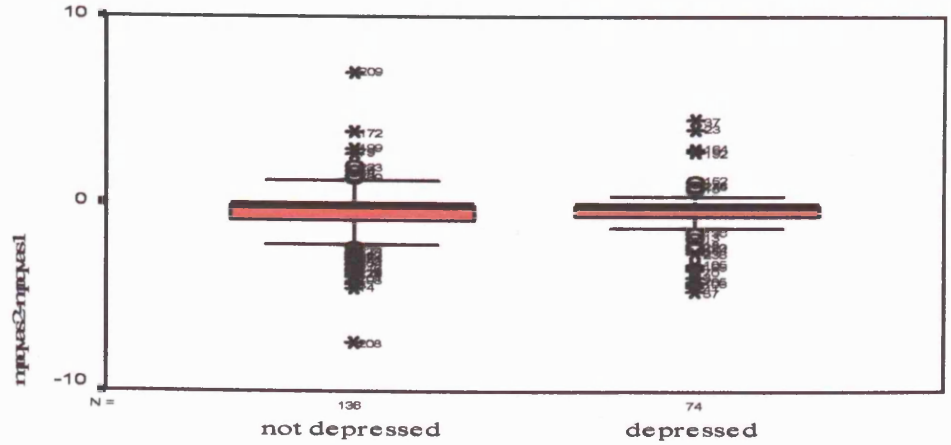
Change in MPI -life control three months

Table 48: McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale.(Kellner)

A comparison of median scores (25th and 75th percentiles) Intention to treat analysis (Depressed and non depressed groups

Self report Questionnaire	Study	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=58)		Group 4=(n=60)	
		Depressed	Non depressed	Depressed	Non depressed	Depressed	Non depressed	Depressed	Non depressed	Depressed	Non depressed
MPQ											
Visual analogue scale (VAS) (range 0-10)	Start	4.2 (1.6,6.7)	2.6 (1.03,4.6)	3.5 (1.15,6.63)	2.8 (1.23,5.25)	3.05 (1.23,5.68)	3.3 (1.48,5.33)	4.5 (2.5,5.8)	2.2 (1,4.05)	4.7 (2.1,7.4)	2.2 (0.5,3.95)
	Finish	3.2 (1.2,5.7) *	2.0 (0.63,4.0) ***	4.15 (0.5,6.03)	2.3 (0.83,3.68)	2.5 (1.38,4.68)	2.5 (0.5,5.6) *	3.35 (0.93,5.08)	1.5 (0.7,3.2) p=0.05	4.5 (1.3,7.6)	1.85 (0.5,3.63)
Present pain intensity (PPI) (range 0-5)	Start	2.0 (1.0,3.0)	2.0 (1.0,2.0)	2.0 (1.25,3.0)	2.0 (1.0,2.0)	2.0 (1.0,2.0)	2.0 (1.0,2.0)	2.0 (1.0,3.0)	1.0 (1.0,2.0)	2.0 (1.0,3.0)	2.0 (1.0,2.0)
	Finish	2.0 (1.0,2.0) ***	1.0 (1.0,2.0) ***	2.0 (1.0,2.0) *	1.0 (1.0,2.0)	2.0 (1.0,2.0) *	1.0 (1.0,2.0)	2.0 (1.0,2.0)	1.0 (1.0,2.0) *	2.0 (1.0,3.0)	1.0 (1.0,2.0) *
MPQ – total % (range 0-100)	Start	42 (29,53)	27.0 (17.5,37.0)	44.0 (29.0,51.0)	31.0 (20,44)	36.0 (31,51)	24 (18,37)	38 (31,51.5)	27 (17,36)	50 (25.25,68.25	22 (11,33.5)
	Finish	33 (18,51) **	22.0 (11.5,36.0) ***	42.0 (22,53)	27.0 (18,40)	31 (18,38) *	26.5 (9,36)	33 (28.5,56.5)	19 (13,31) **	31 (16,64)	16.5 (7.75,36)
MPQ– sensory % (range 0-100)	Start	42 (30,58)	30.0 (18,40.5)	39.0 (24,51.5)	39.0 (27,48)	45.0 (30,54)	30 (17.5,37.5)	45 (31.5,63.5)	30 (18,39)	45 (29.25,70.75	24 (14.25,39.75
	Finish	33 (18,55) **	25.5 (15,39) **	33.0 (15,52)	34.5 (21,42)	33 (21,45) *	28.5 (12,39)	39 (25.5,64.75	21 (15,35.25) *	36 (15,67)	21 (10.5,42)
MPQ – affective % (range 0-100)	Start	42 (17,58)	17.0 (0,25)	42.0 (25,67)	8.0 (0,42)	17 (17,42)	17 (0,29)	25 (17,46)	17 (0,25)	54 (14.75,75.75	8.0 (0,25)
	Finish	25 (9,58) **	8.0 (0,25)	33.0 (17,58) *	7.0 (0,25)	17 (8,33) *	8 (0,25) *	25 (14.75,67)	8 (0,25) *	42 (8,58)	0 (0,17)

Self report questionnaire	Study	All groups (n=237)		Group 1 (n=60)		Group 2 (n=59)		Group 3 (n=58)		Group 4 (n=60)	
		Depressed	Non Depressed	Depressed	Non Depressed	Depressed	Non Depressed	Depressed	Non Depressed	Depressed	Non Depressed
BDI											
Composite score (range 0-45)	Start Finish	16.5 (11.3,21.8) 14 (11,21) **	4.0 (1,7) 4.0(2,7)	16 (11,19) 13 (10,16.8) *	4.0(1,6) 4.0(1,6)	17 (11,24) 12 (11,20) *	5.0(2,7.8) 5.0(1,7)	18(12,26.5) 18(12,25.8)	3.0(1,7) 3.0(0.5,5.5)	16.5(11.3,21)) 14.0(11.0,22)	5.0 (3,8) 4.0 (3,7)
Kellner											
Illness attitude- total (range 0-30)	Start Finish	10 (7,14) 10 (7,13.5)	7.0 (6,9) 7.0 (6,9)	11.0(6,15) 11.0 (6,14)	7.0 (6,9) 7.0 (6,9)	9.0 (7,13) 9.0 (7,12)	6 (6,8) 6 (6,8)	10(6,14) 10(6,13.75)	7.0(6,9.5) 7.0 (6,9)	11.0(6.8,15.3) 12.0 (9,16)	7.5(6,10.8) 7.0(6,9)
Hypochondriacal beliefs (range 0-15)	Start Finish	5 (3,7) 5 (3,7)	3.0 (3,5) 3.0 (3,4) *	5.0 (3,7.75) 5.0 (3,8)	3.0 (3,4.8) 3.0 (3,4)	5.0 (3,7) 5.0 (3,7)	3.0 (3,3.8) 3.0 (3,3.8)	5.0 (3,7) 5.0 (3,7)	3.0 (3,5) 3.0 (3,5)	6.0 (3,7) 6.0 (3,7)	3.0 (3,4) 3.0 (3,4)
Disease phobia (range 0-15)	Start Finish	4 (3,7) 5 (3,7)	3.0 (3,5) 3.0 (3,5)	5.0 (3,8) 5.0 (3,8)	3.0 (3,4) 3.0 (3,4)	4.0 (3,5) 4.0 (3,5)	3.0 (3,4) 3.0 (3,4)	4.5 (3,7) 4.5 (3,7)	3.0 (3,5) 3.0 (3,4)	5.0 (3,9) 5.0 (4,9)	3.5 (3,6.75) 3.0 (3,5.75)



Change in MPQ VAS at three months

Figure 52

Group 1 – Fluoxetine medication Group 2 – Placebo medication
Group 3 – Splint therapy Group 4 – Fluoxetine and splint therapy

Kruskall-Wallis not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p<0.001$***

There was no statistically significant difference between groups in the recorded pain questionnaire scores, although there was an observable decrease, illustrated graphically between groups, in MPQ-VAS (figure52) MPI severity and MPI affective distress (figures 51).

8.2 THE EFFECT OF INITIALLY HIGH PAIN SCORES ON OUTCOME

8.2.0 The effect of high initial pain scores on outcome measures

Hypothesis (6b) A significant and measurable improvement in pain measures are only seen in those patients with initially high pain scores.

8.2.1 Baseline pain severity scores

Figure 53 shows the MPI pain severity scores at baseline and VAS scores were normally distributed. Bivariate, nonparametric, correlations of initial VAS severity scores and initial MPI severity scores revealed significant correlations at the 0.01 level on a range of variables.

VAS was positively correlated with baseline BDI ($r=0.186, p=0.004$), MPI scores of: pain severity ($r=0.313, p<0.001$),interference ($r=0.386, p<0.001$),affective distress ($r=0.241, p<0.001$), support ($r=0.163, p=0.014$),MPQ scores of: PPI ($r=0.267, p<0.001$), total ($r=0.418, p<0.001$),sensory ($r=0.315, p<0.001$) and affective ($r=0.407, p<0.001$). There was a negative correlation with MPI level of life control ($r=-0.213, p=0.001$).

MPI severity scores were positively correlated with baseline BDI ($r=0.313, p<0.001$), VAS ($r=0.498, p<0.001$),MPI scores of: interference ($r=0.668, p<0.001$),affective distress ($r=0.354, p<0.001$), support ($r=0.286, p<0.001$),solicitous ($r=0.191, p=0.005$), distracting response ($r=0.138, p=0.046$), MPQ: PPI ($r=0.600, p<0.001$),total ($r=0.589, p<0.001$), sensory ($r=0.522, p<0.001$),affective ($r=0.520, p<0.001$),Kellner illness attitude ($r=0.151, p=0.019$) and hypochondriacal beliefs ($r=0.154, p=0.017$). MPI life control was negatively correlated ($r=-0.282, p<0.001$).

8.2.2 MPI severity gauge for low and high initial pain scores

MPI severity scores at baseline was normally distributed and more closely correlated to a broader range of outcome variables. It was therefore decided to use this measure to

demarcate individuals into high and low initial pain categories.

High category were classified as those with scores greater than 3 whilst the low category were scores of 0-3. Although a rather arbitrary division, this successfully classified patients into two dichotomous groups, high (n=78) and low (n=171),(fig 54). These was no significant difference in the two categories between the four treatment groups, χ^2 =6.87 (3),p=0.08,(fig. 55, table 49).

Figure 53: Baseline pain scores (MPI severity and VAS)

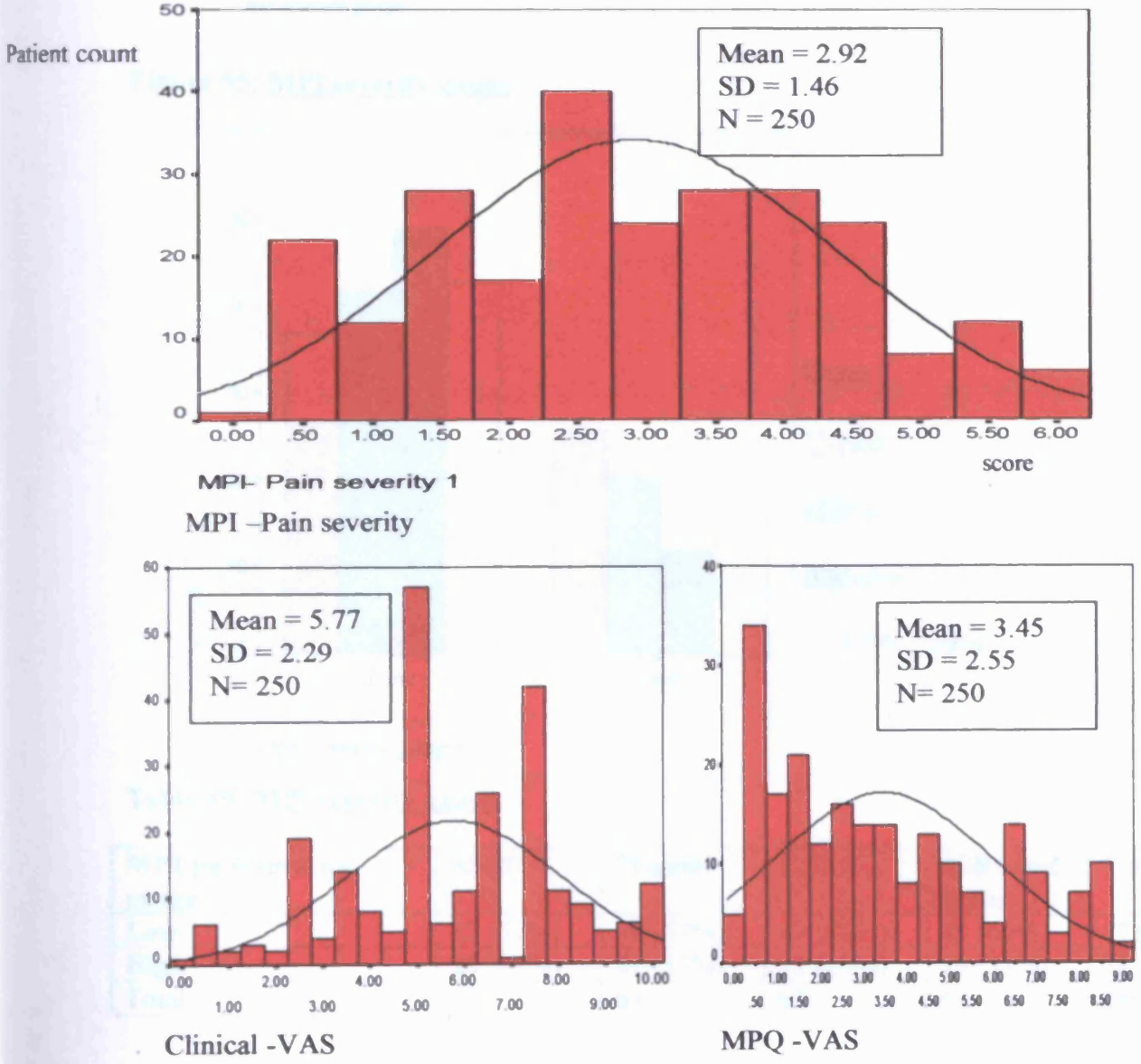
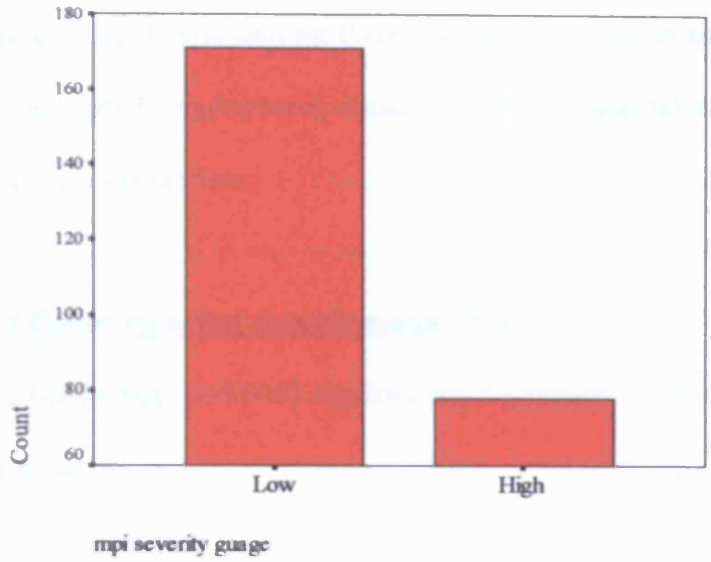


Figure 54: MPI severity gauge (all groups n=249)



Low (n=171)

High (n=78)

Figure 55: MPI severity gauge

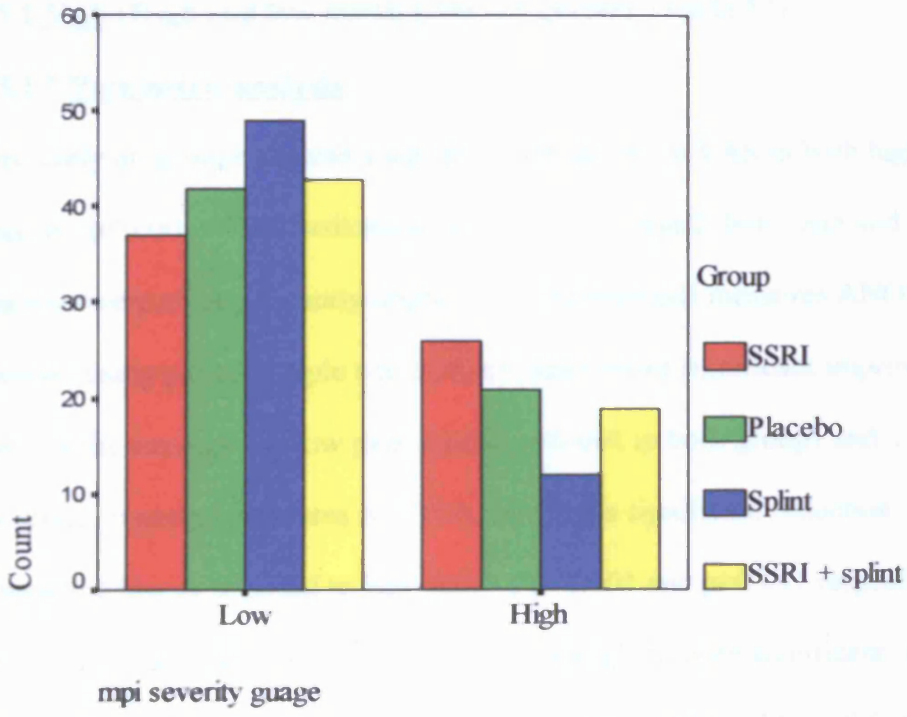


Table 49: MPI severity gauge

MPI pain severity guage	SSRI	Placebo	Splint	SSRI and Splint	Total
Low	32 (51%)	42 (67%)	49 (80%)	43 (69%)	171
High	26 (41%)	21 (33%)	12 (20%)	19 (31%)	78
Total	63	63	61	62	249

8.2.3 Demographic details (initial high and low pain score patients) (Table 50)

Demographic details suggest there was no difference in age, gender, duration of pain, referral source, employment, socio-economic or marital status between high and low initial pain categories.

8.2.4 Other reported chronic pains (Table 51)

Only headaches (p=0.008) significantly decreased in the low compared to the high pain scorers.

8.2.5 Verbal reported pain scores

8.2.5.1 VAS (High and low initial pain categories) (Table 52)

8.2.5.1.1 Parametric analysis

Collectively all groups showed a significant reduction in VAS in both high and low categories p<0.001. With medication only, groups 1 and 2, both high and low categories were all significantly improved in the repeated measures ANOVA p=0.001. However, using paired sample t-tests, there was a more significant improvement at three months amongst the low pain scorers p<0.001 in both group1 and 2. In the splint only group, repeated measures ANOVA revealed a significant reduction in score amongst the low as opposed to high scorers p<0.001 and p=0.011 respectively. This was not mirrored in group 4 where there was a slightly more significant improvement amongst the high compared to low scorers, p=0.003 compared to p=0.005.
Overall, there was no significant difference between groups in high and low scores at any time point.

8.2.5.1.2 Non parametric analysis

Analysing all groups together, a highly significant reduction in scores were seen amongst both high and low initial pain categories, $p<0.001$. At three months this was reflected in group2 and group4. In group 1 the high pain group showed a significant reduction $p<0.001$, low pain $p<0.005$. Conversely, in group 3 it was the low pain group which showed the most significant reduction $p<0.005$, the high group $p<0.05$.
Inter group analysis revealed no significant difference in improvement between groups.

8.2.5.2 Interference (High and low pain categories) (Table 53)

This was significantly reduced amongst both high and low initial pain score categories $p<0.001$.This did not appear to be reflected amongst individual groups. In group 2, 3, 4 low pain scorers improved significantly at all three time points $p<0.001$.High pain scorers decreased but to a lesser extent at three months group 3 and group 4 $p<0.005$.In group 1 both categories had improved $p<0.001$ at three months although at the earlier time points of four and eight weeks the high pain group decreased to a lesser extent $p<0.005$ compared to the low pain category $p<0.001$.

Table 50: Demographic details for initial high and low pain score patients
(MPI severity guage)

Recorded at baseline assessment	All groups (n=250)	**High pain scores (n=78)**	**Low pain scores (n=171)**	Significance
Age (in years) Mean (+/- SD) (Range)	 32.3 (9.58) (16-55)	 31.73 (8.99) (16-54)	 32.51 (9.86) (16-55)	 **ns** (p=0.550)
Duration of pain (in yrs) Mean (+/- SD) Range	 3.30 (4.49) (0.25-32.0)	 2.53 (2.72) (0.25-16.0)	 3.64 (5.08) (0.25-32.0)	 **ns** (p=0.070)
Gender M: F	59: 191 23.6%:76.4%	17: 61 21.8%: 78.2%	42:129 24.6%: 75.4%	**ns** (p=0.634)
Referral source GDP GP Specialist	 230 (92.0%) 6 (2.4%) 14 (5.6%)	 72 (92.3%) 2 (2.6%) 4 (5.1%)	 157 (91.8%) 4 (2.3%) 10 (5.8%)	 **ns** (p=0.969)
Employment status Employed Unemployed Student Retired(medical) House wife	 167 (66.8%) 19 (7.6%) 39 (15.6%) 1 (0.4%) 24 (9.6%)	 56 (71.8%) 6 (7.7%) 9 (11.5%) 0 (0%) 7 (9.0%)	 111 (64.9%) 12 (7.0%) 30 (17.5%) 1 (0.6%) 17 (9.9%)	**ns** (p=0.708)
Socio-economic status Professional I Intermmediate IIi Skilled non-manual IIii Skilled manual III Semi skilled IV Unskilled V Unemployed, house wife, student, retired VI	 11 (4.4%) 78 (31.2%) 66 (26.4%) 8 (3.2%) 5 (2.0%) 1 (0.4%) 81 (32.4%)	 4 (5.1%) 25 (32.1%) 20 (25.6%) 4 (5.1%) 2 (2.6%) 1 (1.3%) 22 (28.2%)	 7 (4.1%) 53 (31.0%) 46 (26.9%) 4 (2.3%) 3 (1.8%) 0 (0%) 58 (33.9%)	**ns** (p=0.691)
Marital status Single Married Seperated Divorced Widowed	 147 (58.8%) 89 (35.6%) 2 (0.8%) 11 (4.4%) 1 (0.4%)	 51 (65.4%) 25 (32.1%) 1 (1.3%) 1 (1.3%) 0 (0%)	 96 (56.1%) 63 (36.8%) 1 (0.6%) 10 (5.8%) 1 (0.6%)	**ns** (p=0.439)

Significance test, Chi-squared (Independent samples t-test for age and duration)
** $p<0.005$, * $p<0.05$, ns=not significant.

Table 51: Other reported chronic pains (MPI severity gauge)

Chronic pains		**Low initial pain** (n=171)	**High initial pain** (n=78)	Significance (between groups)
Headache	Baseline	98 (57.3%)	54 (69.2%)	
	4 weeks	78 (45.6%) *	42 (53.8%) **	ns p=0.228
	8weeks	75 (43.9%) **	51 (65.4%)	**p=0.002
	12 weeks	68 (39.8%) ***	45 (57.7%) *	* p=0.008
		***	*	
Migraine	Baseline	51 (29.8%)	31 (39.7%)	
	4 weeks	31 (18.1%)***	18 (23.1%)**	ns p=0.362
	8weeks	31 (18.1%)***	17 (21.8%)**	ns p=0.496
	12 weeks	28 (16.4%)***	17 (21.8%)**	ns p=0.303
		***	***	
Neckache	Baseline	85 (49.7%)	40 (51.3%)	
	4 weeks	56 (32.7%)***	33 (42.3%)	ns p=0.144
	8weeks	62 (36.3%)***	31 (29.7%)	ns p=0.598
	12 weeks	49 (28.7%)***	28 (35.9%)*	ns p=0.251
		***	*	
Backache	Baseline	77 (45.0%)	43 (55.1%)	
	4 weeks	48 (28.1%)***	26 (33.3%)***	ns p=0.399
	8weeks	47 (27.5%)***	28 (35.9%)***	ns p=0.180
	12 weeks	47 (27.5%)***	26 (33.3%)***	ns p=0.347
		***	***	
Abdominal pain	Baseline	52 (30.4%)	21 (26.9%)	
	4 weeks	24 (14.0%)***	13 (16.7%)**	ns p=0.588
	8weeks	25 (14.6%)**	14 (17.9%)**	ns p=0.503
	12 weeks	24 (14.0%)***	17 (21.8%)*	ns p=0.126
		***	ns p=0.095	

Table 52 : High and low pain scores - Imputation analysis

Pain response: **VAS (visual analogue scale)**,(10cm line) . A comparison of mean scores (+/- SD)

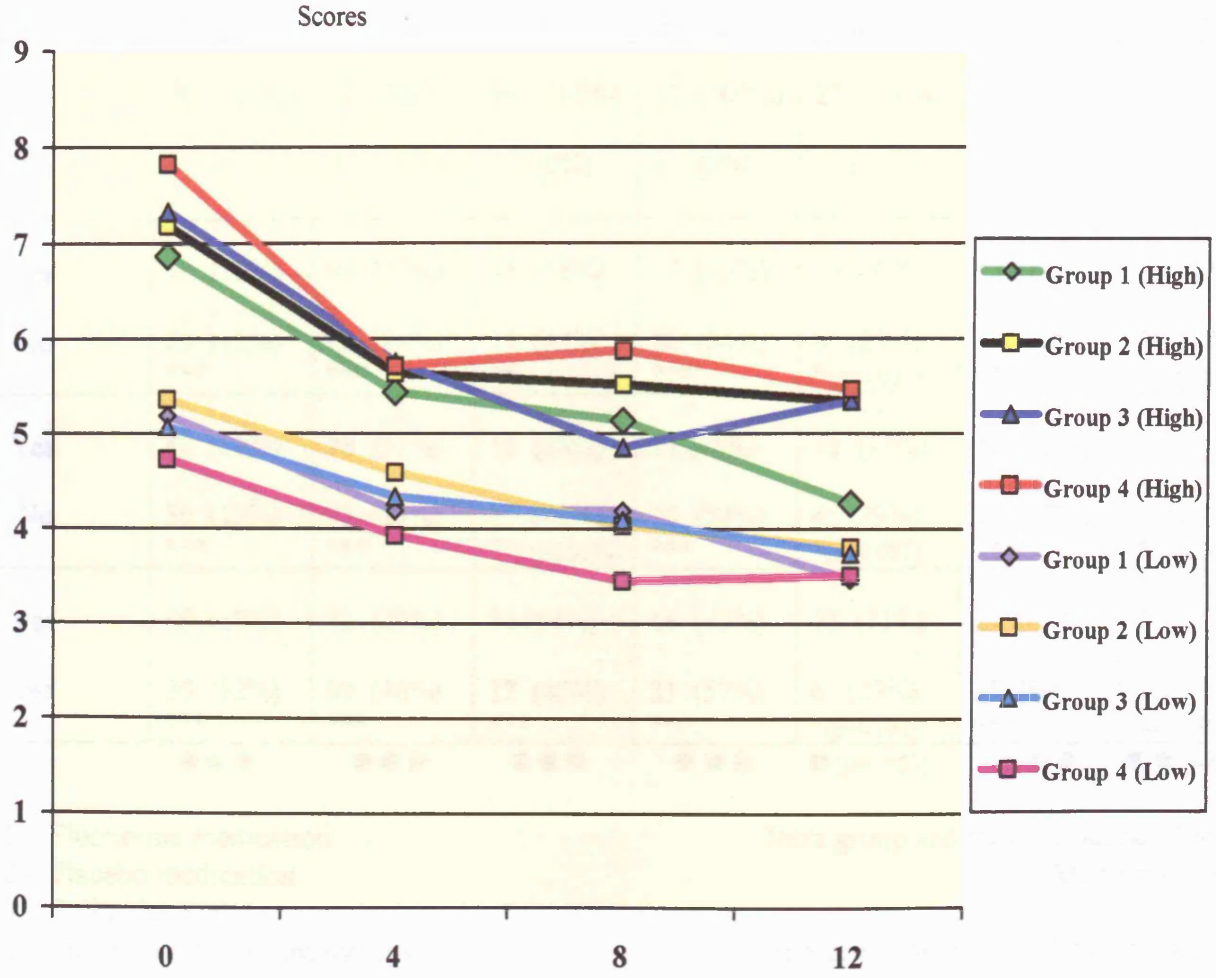
Week	All groups (n= 249)		Group 1 (n=63)		Group 2 (n=63) Low		Group 3 (n=61)		Group 4 (n=62)		Significance between groups	
	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low
0	7.26 (1.95)	5.08 (2.11)	6.87 (2.29)	5.19 (2.07)	7.19 (1.71)	5.36 (2.37)	7.33 (2.20)	5.07 (1.92)	7.83 (1.46)	4.73 (2.09)	**ns** p=0.451	**ns** p=0.565
4	5.61 (2.51) ***	4.27 (1.97) ***	5.44 (2.79) * p=0.028	4.19 (2.09) * p=0.014	5.64 (2.02) ** p=0.003	4.59 (2.19) p=0.07	5.76 (3.05) * p=0.044	4.34 (1.66) * p=0.006	5.72 (2.43) ***	3.93 (1.95) * p=0.029	**ns** p=0.979	**ns** p=0.464
8	5.38 (2.67) ***	3.94 (2.20) ***	5.14 (2.98) * p=0.017	4.19 (2.39) * p=0.028	5.52 (2.14) ** p=0.001	4.03 (2.28) * p=0.005	4.86 (2.87) ** p=0.001	4.09 (2.09) ** p=0.001	5.88 (2.73) ** p=0.003	3.45 (2.08) ** p=0.004	**ns** p=0.714	**ns** p=0.409
12	5.02 (2.82) ***	3.64 (2.33) ***	4.27 (3.08) ** p=0.001	3.47 (2.59) ***	5.34 (2.66) * p=0.005	3.80 (2.22) ***	5.35 (3.06) * p=0.029	3.74 (2.12) ***	5.47 (2.45) * p=0.005	3.51 (2.49) * p=0.011	**ns** p=0.438	**ns** p=0.893
	✱✱✱	✱✱✱	✱✱ p=0.001	✱✱ p=0.001	✱✱ p=0.001	✱✱ p=0.001	✱ p=0.011	✱✱✱	✱✱ p=0.003	✱ p=0.005		

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Repeated measures ANOVA ✱✱✱P<0.0001 ✱✱P<0.005 ✱P<0.05
Paired sample t-test p<0.05 * p<0.005 ** p<0.001***
Inter group analysis: One-way ANOVA not significant

Figure 56: **VAS (visual analogue scale)** A comparison of mean scores

High and low pain scorers (High n=171, low n=78)



Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint

Table 53: Severity guage,initial high and low pain scores - Interference with life (Imputation analysis)

Week	Interference	All groups (n=249)		Group 1 (n=63)		Group 2 (n=63)		Group 3 (n=61)		Group 4 (n=62)	
		High (n=78)	Low (n=171)	High (n=26)	Low (n=37)	High (n=21)	Low (n=42)	High (n=12)	Low (n=49)	High (n=19)	Low (n=43)
0	Yes	78 (100%)	171 (100%)	26 (100%)	37 (100%)	21 (100%)	42 (100%)	12 (100%)	49 (100%)	19 (100%)	43 (100%)
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4	Yes	49 (20%)	93 (37%)	15 (58%)	17 (46%)	15 (71%)	26 (62%)	5 (42%)	25 (51%)	14 (74%)	25 (58%)
	No	29 (12%) ***	78 (31%) ***	11 (42%) **(p=0.001)	20 (54%) ***	6 (29%) *(p=0.031)	16 (38%) ***	7 (58%) *(p=0.016)	24 (49%) ***	5 (26%) ns (p=0.063)	18 (42%) ***
8	Yes	48 (19%)	78 (31%)	15 (58%)	17 (46%)	15 (71%)	18 (43%)	6 (50%)	25 (51%)	12 (63%)	18 (42%)
	No	30 (12%) ***	93 (37%) ***	11 (42%) **(p=0.001)	20 (54%) ***	6 (29%) *(p=0.031)	24 (57%) ***	6 (50%) *(p=0.031)	24 (49%) ***	7 (37%) *(p=0.016)	25 (58%) ***
12	Yes	48 (19%)	72 (29%)	14 (54%)	16 (43%)	15 (71%)	17 (41%)	7 (58%)	22 (45%)	12 (63%)	17 (40%)
	No	30 (12%) ***	99 (40%) ***	12 (46%) ***	21 (57%) ***	6 (29%) *(p=0.031)	25 (59%) ***	5 (42%) ns (p=0.063)	27 (55%) ***	7 (37%) *(p=0.016)	26 (60%) ***
		***	***	***	***	*(p=0.023)	***	**(p=0.001)	***	*(p=0.005)	***

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Cochran Test P<0.001 ***
McNemar Test P<0.001 ***

Intergroup analysis : Chi squared test

8.2.6 Self Report Pain questionnaires (high and low pain severity gauge)

8.2.6.1 MPI (High and low pain severity gauge at baseline) (Table 54)

The patient's perspective of pain had significantly improved during the three months treatment phase in severity, interference, life control and affective distress, amongst all those with initially high pain scores $p<0.001$. Low initial pain scores also improved but to a lesser extent in some fields; severity $p<0.001$, interference $p=0.001$ and affective distress $p=0.006$.

This pattern was reflected in the significant improvement of initial high scorers in group 1 severity $p=0.003$, interference $p=0.002$, life control $p=0.012$ and affective distress $p=0.011$ with no significant change in low scorers. In group 2 and 3 the severity improvement was significant in both groups. In group 2 high ($p=0.002$), low ($p=0.012$), group 3 high ($p=0.043$), low ($p=0.007$). However, interference only improved in low scorers in group 3, $p=0.033$ and high scorers in group 2, $p=0.002$.

The response of significant others revealed support response improved in low severity group 3, $p=0.009$, punishing response increased in high severity group 1, $p=0.010$. These differences, amongst therapeutic groups, were not statistically confirmed in rigorous inter group analysis.

8.2.6.2 MPQ (High and low pain severity gauge) (Table 55)

Together the groups showed significant improvement amongst the low pain scorers in VAS,($p<0.001$) and PPI, ($p<0.001$). This was reflected to a lesser extent in high pain scorers VAS, ($p=0.017$) and PPI, ($p=0.004$). MPQ total % decreased with comparable significance amongst both high and low pain scorers, ($p<0.001$). MPQ sensory % and affective % although significantly reduced in both groups showed slightly increased

improvement amongst the high category p=0.001 and p<0.001 compared to p=0.005 and p=0.005 in the low category respectively.

Within group analysis revealed an interesting observation. Amongst groups 1 and 2 it was only the high initial scorers who showed significant improvement whilst groups 3 and 4 only showed significant improvement in the low pain scorers. In group 1, high pain scorers revealed reduced values in PPI, p=0.017, MPQ tota l%, p=0.015, MPQ sensory %, p=0.025 and MPQ affective %, p=0.036. In group 2, high pain scorers had reduced values in VAS, p=0.01, MPQ total %, p=0.005, MPQ sensory %, p=0.012 and MPQ affective %, p=0.018.Conversely in group 3 it was the low scorers who showed significant improvement in VAS, p=0.009, PPI, p=0.005, MPQ total%, p=0.003 and MPQ sensory %, p=0.009. In group 4 the low scorers only showed significant improvement in PPI, p=0.024.

8.2.6.3 BDI (High and low pain severity scores) Table 55

The composite scores amongst all groups decreased significantly amongst the low scorers, p=0.001, reflected to a lesser extent in group 3, p=0.025.

8.2.6.4 Kellner (High and low pain severity scores) Table 55

Illness attitude and hypochondriacal beliefs only significantly decreased amongst the high scorers, p=0.026 and p=0.024 respectively. Intra group analysis revealed no significant differences.

8.2.6.5 Intergroup analysis

In the intergroup analysis, despite the interesting trends in the MPI and MPQ scores there was no significant difference observed in MPI, MPQ, BDI or Kellner to clearly distinguish between the four groups.

Table 54: Multidimensional pain inventory (MPI) (Pain severity gauge, high and low initial pain scores)
A comparison of median scores (25^{th},75^{th} percentiles) between the start and finish of the three months.

MPI	Study	All groups (n=249)		Group 1 (n=63)		Group 2 (n=63)		Group 3 (n=61)		Group 4 (n=62)	
		High	Low	High	Low	High	Low	High	Low	High	Low
Patients perspective of pain											
MPI - Severity	Start	4.60 (4.00,5.00)	2.33 (1.33,3.00)	4.6 (4.0,5.0)	2.00 (1.47,3.0)	4.33 (4.00,4.66)	2.60 (1.66,3.00)	4.50 (4.00,5.75)	2.33 (1.15,3.00)	5.00 (4.00,5.33)	2.00 (1.30,3.00)
	Finish	4.00 (2.66,4.66) ***	2.00 (1.00,2.66) ***	4.0 (2.45,4.66) **(p=0.003)	1.66 (1.0,3.0) ns(p=0.248)	4.00 (2.50,4.33) **(p=0.002)	2.16 (1.00,2.75) * (p=0.012)	4.32 (3.25,4.66) *(p=0.043)	2.00 (0.66,2.66) * (p=0.007)	4.00 (3.60,5.30)	2.00 (1.30,2.33)
MPI - Interference	Start	3.18 (2.09,4.18)	1.0 (0.45,1.63)	3.10 (2.47,4.05)	1.09 (0.55,1.62)	3.27 (1.78,4.14)	1.09 (0.52,1.90)	3.09 (1.90,4.55)	1.00 (0.38,1.99)	3.81 (1.36,4.36)	0.90 (0.30,1.45)
	Finish	2.59 (1.07,4.00) ***	0.80 (0.30,1.73) ** (p=0.001)	2.540 (0.54,3.89) ** (p=0.002)	0.82 (0.25,1.81) ns(p=0.086)	2.54 (1.09,3.86) **(p=0.002)	0.81 (0.36,1.75) ns (p=0.070)	2.23 (0.91,4.05) ns (p=0.273)	0.70 (0.27,2.14) * (p=0.033)	3.09 (1.09,4.27)	0.64 (0.36,1.33)
MPI – Life control	Start	2.50 (1.50,3.50)	3.50 (2.75,4.25)	2.63 (1.44,3.56)	3.50 (2.75,4.50)	2.75 (1.50,3.88)	3.38 (2.50,4.25)	2.29 (2.00,3.13)	3.50 (2.75,4.13)	2.50 (1.75,3.50)	3.75 (3.00,4.50)
	Finish	3.00 (1.75,3.75) **(p=0.003)	3.66 (2.75,4.25) * (p=0.023)	3.50 (1.50,4.06) * (p=0.012)	3.75 (2.88,4.75) ns(p=0.055)	3.25 (2.40,4.68)	3.75 (2.69,4.06)	2.38 (2.00,3.63)	3.50 (2.75,4.25)	2.50 (1.50,3.50)	3.75 (3.00,4.50)
MPI –Affective distress	Start	4.00 (3.32,5.00)	3.00 (2.23,4.00)	4.00 (3.25,5.08)	3.30 (2.32,4.30)	4.00 (3.15,4.83)	3.33 (2.17,4.00)	3.83 (3.33,5.00)	3.00 (2.00,3.66)	4.00 (3.30,5.33)	2.66 (2.30,4.00)
	Finish	3.66 (2.60,4.62) ***	3.00 (2.00,3.66) **(p=0.006)	3.63 (2.37,4.15) * (p=0.011)	3.00 (1.83,4.00) ns(p=0.070)	3.60 (2.15,4.48) * (p=0.023)	3.30 (2.00,3.66) ns (p=0.064)	3.83 (2.87,4.83)	3.00 (1.66,3.83)	3.33 (2.33,5.33)	2.60 (1.66,3.33)
Response of significant other											
MPI – Support response	Start	4.00 (3.00,5.15)	3.00 (2.00,4.33)	4.33 (3.0,5.15)	2.60 (1.15,4.00)	4.60 (3.15,6.00)	3.00 (2.00,4.25)	3.33 (2.13,4.50)	3.00 (2.25,4.41)	3.33 (1.57,5.08)	3.00 (2.32,4.33)
	Finish	4.00 (3.00,4.66)	3.00 (2.00,4.00)	4.00 (3.33,4.66)	2.83 (1.00,4.00)	4.60 (3.15,5.65)	3.00 (1.66,4.33)	3.66 (2.66,4.33) ns (p=0.655)	3.00 (1.60,4.00) * (p=0.009)	3.66 (1.92,4.75)	3.33 (2.33,4.00)

MPI		All groups (n=249)		Group 1 (n= 63)		Group 2 (n= 63)		Group 3 (n=61)		Group 4 (n= 62)	
	Study	High	Low	High	Low	High	Low	High	Low	High	Low
MPI Punishing response	Start	1.00 (0.25,2.25)	1.00 (0,2.0)	0.50 (0,2.63)	1.0 (0.5,3.13)	1.38 (0.50,2.75)	1.25 (0.06,2.44)	0.25 (0,1.44)	0.88 (0.63,2.25)	1.50 (0.19,2.37)	0.75 (0,1.25)
	Finish	1.25 (0.25,2.25)	1.00 (0,2.00)	1.25 (0.38,2.75) * (p=0.010)	0.88 (0,2.56) ns (p=0.072)	1.25 (0.50,2.00)	1.25 (0.06,2.38)	0.75 (0.19,1.44)	1.00 (0,2.06)	1.50 (0.19,2.50)	0.75 (0,1.25)
MPI Solicitous response	Start	3.00 (1.33,4.83)	2.63 (1.5,3.53)	3.00 (1.45,4.58)	2.33 (1.40,3.42)	3.38 (2.62,5.20)	2.63 (1.08,3.46)	3.08 (1.53,4.36)	2.66 (1.50,3.42)	1.97 (0.77,3.95)	2.55 (1.55,4.00)
	Finish	3.00 (1.60,4.50) ns(p=0.791)	2.50 (1.16,3.50) *(p=0.039)	3.00 (1.72,4.75)	2.33 (1.16,3.37)	3.16 (2.00,5.16)	2.50 (1.00,3.53)	3.08 (1.42,4.16)	2.63 (1.50,3.50)	2.33 (0.83,3.83)	2.50 (1.50,3.50)
MPI Distracting response	Start	2.00 (1.00,3.00)	1.75 (0.75,2.75)	1.75 (0.63,2.75)	2.00 (1.00,2.63)	2.13 (1.00,3.56)	1.50 (0.75,2.63)	2.63 (0.94,3.06)	1.63 (0.50,2.75)	1.88 (0.44,3.06)	1.75 (0.38,2.88)
	Finish	2.25 (1.00,3.00)	1.50 (0.75,2.75)	2.25 (0.63,3.25)	1.75 (1.00,2.56)	2.25 (1.00,3.50)	1.38 (0.50,2.44)	2.63 (0.69,3.06)	1.75 (0.75,2.75)	1.88 (0.88,3.00)	1.75 (0.50,3.00)
Frequency of participation											
MPI – Household chores	Start	4.80 (3.60,5.90)	4.80 (3.40,5.60)	4.50 (3.15,5.55)	5.00 (4.00,5.60)	4.50 (3.60,5.95)	4.80 (3.20,5.65)	5.00 (3.65,5.85)	4.50 (3.35,5.80)	5.00 (4.20,6.00)	4.80 (3.40,5.25)
	Finish	4.70 (3.60,5.40)	4.60 (3.60,5.60)	4.60 (3.45,5.65)	4.80 (4.20,5.40)	4.60 (3.30,5.70)	4.30 (3.40,5.60)	4.90 (3.95,5.40)	4.40 (3.60,5.60)	4.8 (3.8,5.4) *	4.60 (3.40,5.60)
MPI – Outdoor work	Start	1.66 (1.00,3.00)	2.00 (1.00,3.00)	1.75 (1.20,3.40)	2.00 (1.40,2.850)	2.60 (1.23,3.40)	1.90 (0.62,2.95)	1.40 (1.00,2.50)	2.0 (0.85,3.00)	0.80 (0.25,3.00)	2.00 (1.23,3.15)
	Finish	2.00 (1.00,3.40)	1.80 (1.00,2.79)	2.20 (1.30,4.00)	1.75 (1.25,2.75)	2.29 (1.35,3.70)	1.90 (0.81,2.46)	1.90 (0.95,2.15)	1.60 (0.68,2.80)	1.67 (0.48,3.35)	2.0 (1.00,3.00)
MPI – Activities away from home	Start	3.75 (2.50,4.25)	3.50 (2.75,4.25)	3.63 (2.25,4.31)	3.50 (2.75,4.38)	4.00 (2.50,4.81)	3.63 (2.94,4.50)	3.75 (2.06,4.00)	3.25 (2.44,4.25)	3.25 (2.50,4.00)	3.75 (2.50,4.75)
	Finish	3.50 (2.50,4.00)	3.50 (2.75,4.50)	3.50 (2.44,4.00)	3.66 (2.75,4.63)	3.75 (2.50,4.50)	3.42 (2.75,4.31)	3.63 (2.63,4.00)	3.50 (2.75,4.25)	3.25 (2.25,3.75)	3.75 (2.75,4.50)
MPI – Social activities	Start	3.25 (2.13,3.75)	3.00 (2.33,4.00)	3.00 (2.25,3.56)	2.71 (2.27,4.25)	3.38 (2.35,4.29)	3.25 (2.50,4.00)	3.50 (1.69,3.94)	3.00 (2.31,3.75)	3.25 (2.00,3.50)	3.50 (2.25,4.25)
	Finish	3.25 (2.00,4.00)	3.25 (2.37,3.75)	3.00 (2.19,4.06)	2.88 (2.33,3.75)	3.25 (2.53,4.25)	3.50 (2.50,4.00)	3.50 (1.44,4.00)	3.00 (2.33,3.50)	3.25 (1.60,3.75)	3.50 (2.50,4.25)
MPI – General activity level	Start	3.44 (2.66,3.91)	3.34 (2.74,3.90)	3.49 (2.52,3.90)	3.38 (2.84,3.88)	3.61 (2.52,4.29)	3.31 (2.68,3.70)	3.51 (2.56,3.81)	3.28 (2.49,3.73)	3.29 (2.75,3.64)	3.36 (2.81,4.06)
	Finish	3.30 (2.70,3.93)	3.30 (2.79,3.76)	3.36 (2.53,3.93)	3.38 (2.74,3.87)	3.53 (2.62,4.55)	3.20 (2.93,3.60)	3.44 (2.87,3.78)	3.24 (2.53,3.68)	3.13 (2.75,3.36)	3.36 (2.85,3.88)

Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p< 0.001$, Kruskall Wallice not significant between groups

Table 55: McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale.(Kellner)
A comparison of median scores (25th and 75th percentiles) Intention to treat analysis (High and low initial pain scores)

Self report Questionnaire	Study	All groups		Group 1		Group 2		Group 3		Group 4	
		High	Low	High	Low	High	Low	High	Low	High	Low
MPQ											
Visual analogue scale (VAS) (range 0-10)	Start	5.8 (3.3,7.5)	2.1 (0.8,3.7)	5.05 (1.73,6.68)	1.95 (0.65,3.65)	5.65 (3.60,7.5)	2.5 (0.93,4.15)	6.5 (2.8,8)	2.2 (1.1,3.85)	6.8 (4.18,7.95)	1.65 (0.5,3.65)
	Finish	5.1 (2.25,6.9) * p=0.012	1.6 (0.5,3.28) ***	4.0 (2.13,6.13)	1.4 (0.5,3.38)	5.0 (1.83,6.08) * p=0.011	1.9 (0.6,4.0)	5.45 (2.63,7.68)	1.4 (0.58,3.2) * p=0.009	6.75 (2.5,8.25)	1.5 (0.5,2.7)
Present pain intensity (PPI) (range 0-5)	Start	2.0 (2.0,3.0)	1.0 (1.0,2.0)	2.0 (1.75,3.0)	2.0 (1.0,2.0)	2.0 (1.5,2.5)	1.0 (1.0,2.0)	3.0 (2,3.75)	1.0 (1.0,2.0)	3.0 (2.0,3.0)	1.0 (1.0,2.0)
	Finish	2.0 (1.0,3.0) ** p=0.004	1.0 (1.0,2.0) ***	2.0 (1.0,2.25) * p=0.017	1.0 (1.0,2.0)	2.0 (1.5,2.5)	1.0 (1.0,2.0) p=0.052	2.5 (1.25,3.0)	1.0 (1.0,2.0) * p=0.005	2.0 (2.0,3.0)	1.0 (1.0,2.0) * p=0.024
MPQ – total % (range 0-100)	Start	44 (29,60)	27.0 (16,36)	38 (27,51)	31 (20,47)	40 (31,58)	27 (18,36)	40 (29,56)	28 (17,36)	57 (39.8,72.3)	22 (13.8,34.5)
	Finish	36 (22,53.75) ***	20 (11,36) ***	33 (22.5,50.5) * p=0.015	24 (12,42)	33.5 (19,38) * p=0.005	26 (12,34.5)	38.5 (27.5,59)	20 (12,32) ** p=0.003	46.5 (17.5,71.3)	18 (10,32)
MPQ– sensory % (range 0-100)	Start	42 (32,67)	30.0 (18,39)	39.0 (30,50)	36 (24,48)	42 (32,57)	30 (17,36)	42 (30,63)	30 (18,39)	62.5 (32.3,74.5)	24 (15.8,39)
	Finish	36 (21,56.5) ** p=0.001	24.0 (13.3,38.5) ** p=0.005	36.0 (24.8,46.5) * p=0.025	30 (13.5,45)	34.5 (21,45) * p=0.012	27 (12,38)	45.5 (27.75,72)	21 (14.5,33) * p=0.009	53.5 (14.3,73.8)	21 (12,40.5)
MPQ – affective % (range 0-100)	Start	42 (17,67)	17.0 (0,25)	42 (8,75)	17 (0,42)	33 (25,58)	17 (0,25)	25 (17,42)	17 (0,25)	58 (42,83)	8.0 (0,25)
	Finish	25 (8,58) ***	8.0 (0,25) ** p=0.005	25 (6.5,67) ** p=0.036	8 (0,25)	21 (10.25,33) * p=0.018	17 (0,25)	17 (17,42)	8 (0,25)	42 (7,75.75)	8.0 (0,17)

Self report questionnaire Study		All groups (n=249)		Group 1 (n=63)		Group 2 (n=63)		Group 3 (n=61)		Group 4 (n=62)	
		High	Low	High	Low	High	Low	High	Low	High	Low
BDI											
Composite score (range 0-45)	Start	10 (6,19)	6.0 (2.75,10.0)	8.0 (3.5,15)	6.00 (2,13)	7.0 (5,16)	7.5 (3,11)	10 (7,21)	5.0 (1.75,9.25)	16 (11,21)	6.0 (3.0,9.0)
	Finish	9.5 (5,17)	5.0 (2.0,10.0) ** p=0.001	7.0 (3.75,12.5)	5.00 (1,13)	7.0 (3.5,10.5)	6.0 (2,11)	11 (5.25,20.8)	3.0 (0.75,8.25) * p=0.025	15 (11,23)	5.5 (3,10.25)
Kellner											
Illness attitude- total (range 0-30)	Start	9.00 (6,14)	7.00 (6,10)	9.0 (7,14)	7.0 (6.0,10.75)	7.0 (6.0,10.0)	7.0 (6.0,9.0)	8.0 (6,10)	7.5 (6,12)	12 (9.5,17)	7.0 (6.0,10.25)
	Finish	9.00 (6,12) * p=0.026	7.00 (6,10)	9.0 (6,14)	6.5 (6,11)	7.0 (6.0,10.0)	7.0 (6.0,9.25)	6.0 (6,8.75)	7.0 (6,11)	12 (9,16)	8.0 (6.0,10.25)
Hypochondriacal beliefs (range 0-15)	Start	4.5 (3.0,7.0)	3.0 (3.0,5.0)	4.0 (3.0,7.0)	3.0 (3.0,5.75)	3.0 (3.0,5.75)	3.0 (3.0,5.0)	3.0 (3.0,7.0)	3.0 (3.0,6.0)	7.0 (4.5,9.0)	3.0 (3.0,5.0)
	Finish	4.0 (3.0,6.5) * p=0.024	3.0 (3.0,5.0)	4.0 (3.0,7.0)	3.0 (3.0,4.75)	3.0 (3.0,5.0)	3.0 (3.0,5.0)	3.0 (3.0,3.75)	3.0 (3.0,5.0)	6.5 (3.75,7.5)	3.0 (3.0,5.0)
Disease phobia (range 0-15)	Start	4.0 (3.0,6.25)	3.0 (3.0,5.0)	4.0 (3.0,6.5)	3.0 (3.0,4.75)	3.5 (3.0,4.0)	3.0 (3.0,4.0)	3.0 (3.0,5.0)	3.0 (3.0,6.0)	5.5 (3.0,9.25)	3.5 (3.0,5.0)
	Finish	4.0 (3,6)	3.0 (3.0,5.0)	3.0 (3.0,7.0)	3.0 (3.0,4.75)	3.0 (3.0,4.5)	3.0 (3.0,4.0)	3.0 (3.0,4.75)	3.0 (3.0,6.0)	5.0 (3.0,9.25)	3.5 (3.0,6.0)

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Kruskall-Wallis not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p<0.001$***

8.3 THE CHARACTERISTICS OF RESPONDERS AND NONRESPONDERS TO TREATMENT

8.3.0 Responders and non responders to therapy (>25% pain improvement)

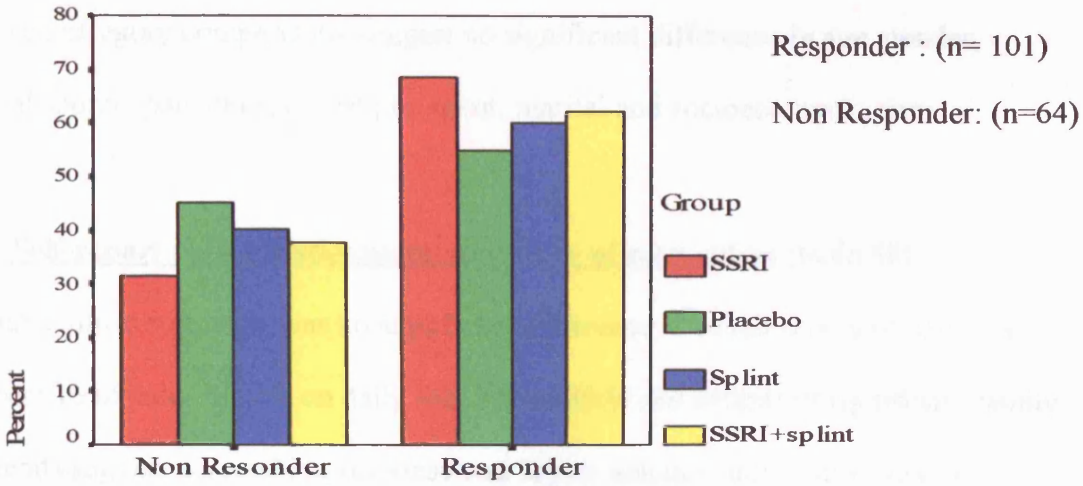
Hypothesis (6c) Clinical and pain history characteristics at baseline separate the treatment responders from the non responders

Treatment responders and non responders were categorised using the primary outcome measure of >25% pain improvement at the end of the three months treatment phase, from the clinical visual analogue scale, using the completers analysis (N=165), (fig.56, table 57), followed by the more rigorous ITT analysis (N=201),(fig57a, table 56a).Demographic, initial self reported pain questionnaires, clinical history and examination findings were analysed to assess differences in those responding positively to therapy, using the ITT analysis.

Table 56: > 25% improvement at three months (Completers) (VAS (clinical)

>25% improvement in VAS (clinical) at 3/12	SSRI	Placebo	Splint	SSRI and Splint	Total
Non Responder	12 (32%)	19 (45%)	16 (40%)	17 (38%)	64
Responder	26 (68%)	23 (55%)	24 (60%)	28 (62%)	101
Total	38	42	40	45	165

Figure 57: > 25% improvement at three months (Completers)

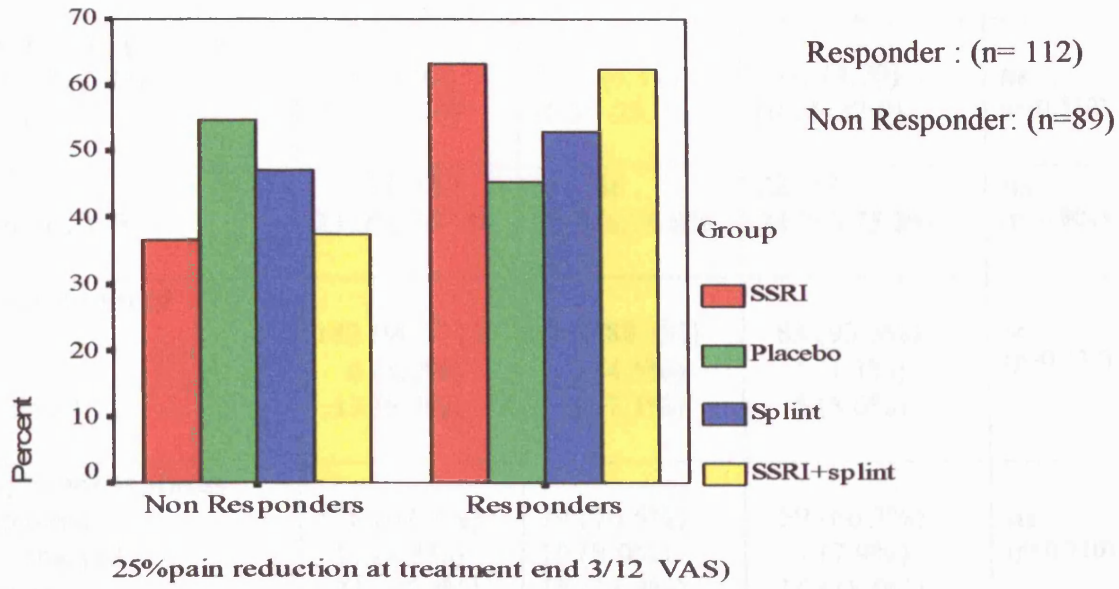


25% pain reduction at treatment end 3/12 (VAS)

Table 56a: > 25% improvement at three months (ITT analysis) VAS (clinical)

>50% improvement in VAS (clinical) at 3/12	SSRI	Placebo	Splint	SSRI and Splint	Total
Non Responder	18 (37%)	29 (55%)	24 (47%)	18 (38%)	89
Responder	31 (63%)	24 (45%)	27 (53%)	30 (63%)	112
Total	49	53	51	48	201

Figure 57b: > 25% improvement at three months (ITT analysis)



25%pain reduction at treatment end 3/12 VAS)

8.3.1 Demographics, summary of responders (table 57)

Between category comparisons suggest no significant difference in age, gender, referral source, pain duration, employment, marital and socioeconomic status.

8.3.2 Self-report pain questionnaire, summary of responders (table 58)

The table illustrates there was no significant difference in initial scores of patient's perspective of pain, impact on daily life. The attitude and actions of significant family or friends suggest a punishing response was higher amongst non responders to therapy,(p=0.017). Frequency of participation in social activities seemed to be higher amongst non responders p=0.011 and so was the general activity level p=0.047.

Table 57:

Demographic details for responders and non responders to treatment (N=201)

Recorded at baseline assessment	All groups (n=201)	**Responders** (n=112)	**Nonresponders** (n=89)	Significance
Age (in years) Mean (+/- SD) (Range)	32.4 (9.78) (16-55)	33.0 (10.28) (16-55)	31.6 (9.13) (16-55)	**ns** (p=0.322)
Duration of pain (in yrs) Mean (+/- SD) Range	3.38 (4.40) (0.25-32.0)	3.19 (4.17) (0.25-25.0)	3.61 (4.70) (0.25-32.0)	**ns** (p=0.510)
Gender M: F	48: 153 23.9%:76.1%	26: 86 23.2%:76.8%	22: 67 24.7%:75.3%	**ns** (p=0.804)
Referral source GDP GP Specialist	 182 (90.5%) 6 (3.0%) 13 (6.5%)	 99 (88.4%) 5 (4.5%) 8 (7.1%)	 83 (93.3%) 1 (1.1%) 5 (5.6%)	**ns** (p=0.339)
Employment status Employed Unemployed Student Retired (medical) House wife	 138 (68.7%) 17 (8.5%) 31 (15.4%) 1 (0.5%) 14 (7.0%)	 79 (70.5%) 10 (8.9%) 15 (13.4%) 0 (0%) 8 (7.1%)	 59 (66.3%) 7 (7.9%) 16 (18.0%) 1 (1.1%) 6 (6.7%)	**ns** (p=0.710)
Socio-economic status Professional I Intermmediate IIi Skilled non-manual IIii Skilled manual III Semi skilled IV Unskilled V Unemployed, house wife, student, retired VI	 7 (3.5%) 66 (32.8%) 56 (27.9%) 7 (3.5%) 3 (1.5%) 1 (0.5%) 61 (30.4%)	 6 (5.4%) 33 (29.5%) 33 (29.5%) 6 (5.4%) 2 (1.8%) 0 (0%) 32 (28.6%)	 1 (1.1%) 33 (37.1%) 23 (25.8%) 1 (1.1%) 1 (1.1%) 1 (1.1%) 29 (32.6%)	**ns** (p=0.252)
Marital status Single Married Seperated Divorced Widowed	 123 (61.2%) 69 (34.3%) 1 (0.5%) 7 (3.5%) 1 (0.5%)	 68 (60.7%) 37 (33.1%) 1 (0.9%) 0 (4.5%) 0 (0.9%)	 55 (61.8%) 32 (36.0%) 0 (0%) 2 (2.2%) 0 (0%)	**ns** (p=0.519)

Significance test, Chi-squared (Independent samples t-test for age and duration)

Table 58: Self -Report Pain Questionnaires at baseline (Responders and Non responders)

MPI	(n=201) All groups	(n=112) Responders	(n=89) Non responders	Significance
Patients perspective of pain and impact on daily life				
MPI - Severity	3.00 (2.00,4.00)	3.00 (2.00, 4.23)	3.00 (1.66, 3.83)	ns (p=0.285)
MPI - Interference	1.45 (0.64,2.90)	1.50 (0.82, 3.19)	1.40 (0.50, 2.41)	ns (p=0.121)
MPI – Life control	3.25 (2.50,4.00)	3.25 (2.50, 4.00)	3.25 (2.29, 4.00)	ns (p=0.810)
MPI – Affective distress	3.33 (2.33,4.30)	3.33 (2.31, 4.30)	3.33 (2.60, 4.30)	ns (p=0.775)
Response of significant other person to patient				
MPI – Support response	3.60 (2.30,4.66)	3.66 (2.60, 4.66)	3.00 (2.00, 4.33)	ns (p=0.198)
MPI – Punishing response	0.75 (0,2.00)	0.50 (0.00, 1.94)	1.25 (0.25, 2.75)	* **(p=0.017)**
MPI – Solicitous response	2.66 (1.50,3.83)	2.83 (1.50, 4.00)	2.66 (1.60, 3.60)	ns (p=0.617)
MPI – Distracting response	2.00 (0.75,3.00)	2.00 (0.75,3.00)	1.75 (0.75, 2.75)	ns (p=0.689)
Frequency of participation in common activities				
MPI – Household chores	4.80 (3.40,5.60)	4.80 (3.20, 5.40)	5.00 (3.65, 5.80)	ns (p=0.112)
MPI – Outdoor work	2.00 (1.00,3.00)	2.00 (1.10, 3.00)	2.00 (1.00, 2.80)	ns (p=0.349)
MPI – Activities away from home	3.50 (2.75,4.50)	3.50 (2.69, 4.25)	3.75 (3.00, 4.69)	ns (p=0.172)
MPI – Social activities	3.25 (2.28,4.00)	3.00 (2.19, 3.75)	3.50 (2.50, 4.25)	* **(p=0.011)**
MPI – General activity level	3.40 (2.75,3.98)	3.30 (2.71, 3.77)	3.57 (2.83, 4.06)	* **(p=0.047)**
MPQ				
Visual analogue scale (VAS) (range 0-10)	3.00 (1.40,5.60)	3.00 (1.48, 5.20)	3.00 (1.10, 5.90)	ns (p=0.835)
Present pain intensity (PPI) (range 0-5)	2.00 (1.00,2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	ns (p=0.779)
MPQ – total % (range 0-100)	29.0 (18.0,42.5)	29.0 (18.00,41.00)	29.0 (20.00,44.00)	ns (p=0.941)
MPQ– sensory % (range 0-100)	33.0 (21.0,45.0)	33.0 (21.0, 45.00)	33.0 (21.00,45.00)	ns (p=0.771)
MPQ – affective % (range 0-100)	17.0 (0,42.0)	17.0 (0.0, 42.00)	17.0 (8.00, 37.50)	ns (p=0.618)
BDI				
Composite score (range 0-45)	7.0 (3.00,12.0)	7.0 (3.00, 15.00)	7.0 (3.00, 11.00)	ns (p=0.653)
Kellner				
Illness attitude- total (range 0-30)	7.0 (6.0,11.0)	7.5 (6.00, 10.75)	7.0 (6.00, 11.00)	ns (p=0.581)
Hypochondriacal beliefs (range 0-15)	3.0 (3.00,6.00)	3.0 (3.00,6.00)	3.0 (3.00,6.00)	ns (p=0.264)
Disease phobia (range 0-15)	3.0 (3.00,6.00)	3.0 (3.00,5.00)	3.0 (3.00, 5.00)	ns (p=0.878)

Table 59a: TMJ symptoms

Baseline record prior to treatment	**All groups** (n=201)	**Responders** (n=112)	**NonResponders** (n=89)	Significance
TMJ symptoms				
TMJ pain	201 (100%)	112 (100%)	89 (100%)	-
Muscle pain – Temporalis	52 (26%)	29 (27.9%)	23 (25.8%)	**ns** (p=0.994)
Muscle pain - Masseter	64 (32%)	31 (26.8%)	33 (37.1%)	**ns** (p=0.155)
Clicking	152 (76.8%)	90 (83.8%)	62 (69.7%)	**ns** (p=0.079)
Sticking	59 (30.4%)	37 (26.5%)	22 (24.7%)	**ns** (p=0.198)
Limitation in mouth opening	35 (74.8%)	20 (67.6%)	15 (16.9%)	**ns** (p=0.852)
Ear popping	36 (20.4%)	21 (20.6%)	15 (16.8%)	**ns** (p=0.798)
Ear buzzing	27 (14.8%)	14 (20.6%)	13 (14.6%)	**ns** (p=0.757)
Ear deafness	30 (14.8%)	18 (19.1%)	12 (13.5%)	* (p=0.045)
Ear fullness	47 (24.8%)	26 (22.1%)	21 (23.6%)	**ns** (p=0.890)
Character of TMJ pain				
Dull ache	132 (65.7%)	71 (63.4%)	61 (68.5%)	**ns** (p=0.445)
Discomfort	109 (54.2%)	59 (52.7%)	50 (56.2%)	**ns** (p=0.621)
Sharp	82 (40.8%)	44 (39.3%)	38 (42.7%)	**ns** (p=0.625)
Stabbing	31 (15.4%)	15 (13.4%)	16 (18.0%)	**ns** (p=0.371)
Throbbing	11 (5.5%)	6 (5.4%)	5 (5.6%)	**ns** (p=0.936)
Burning	3 (1.5%)	3 (2.7%)	0 (0%)	**ns** (p=0.120)
Unilateral	140 (69.7%)	83 (74.1%)	57 (64.0%)	**ns** (p=0.123)

Table 59b: Other reported chronic pains

Recorded at baseline assessment	(n=201) All groups	(n=112) Responders	(n=89) Non responders	Significance
Recurrent chronic pains				
Headache	121 (60.2%)	61 (54.5%)	60 (67.4%)	**ns** (p=0.062)
Migraine	65 (32.3%)	36 (32.1%)	29 (32.6%)	**ns** (p=0.947)
Neck ache	100 (49.8%)	50 (44.6%)	50 (56.2%)	**ns** (p=0.104)
Back pain	94 (46.8%)	57 (50.9%)	37 (41.6%)	**ns** (p=0.188)
Abdominal pain	61 (30.3%)	37 (33.0%)	24 (27.0%)	**ns** (p=0.353)
Pruritus	44 (21.9%)	26 (23.2%)	18 (20.2%)	**ns** (p=0.611)
Chest pain	29 (14.4%)	16 (14.3%)	13 (14.6%)	**ns** (p=0.949)

Table 59c: Onset ,exacerbation and relief of TMJ pain

Base line record	All groups (n=201)	Responders (n=112)	Non Responders (n=89)	Significance
Precipitating factors				
Dental	58 (28.9%)	34 (30.4%)	24 (27.0%)	**ns** (p=0.60)
Physical trauma	31 (15.4%)	16 (14.3%)	15 (16.9%)	**ns** (p=0.62)
Emotional trauma	49 (24.4%)	31 (27.7%)	18 (20.2%)	**ns** (p=0.22)
Infection	5 (2.5%)	3 (2.7%)	2 (2.2%)	**ns** (p=0.85)
None	54 (26.9%)	29 (25.9%)	25 (28.1%)	**ns** (p=0.73)
Provoking factors				
Chewing	152 (75.6%)	83 (74.1%)	69 (77.5%)	**ns** (p=0.58)
Yawning	153 (76.1%)	85 (75.9%)	68 (76.4%)	**ns** (p=0.93)
Biting	129 (64.2%)	70 (62.5%)	59 (66.3%)	**ns** (p=0.58)
Emotional tension	108 (53.7%)	54 (48.2%)	54 (60.7%)	**ns** (p=0.08)
Talking	62 (30.8%)	34 (30.4%)	28 (31.5%)	**ns** (p=0.87)
Cold weather	57 (28.4%)	33 (29.5%)	24 (27.0%)	**ns** (p=0.70)
Hot weather	4 (2.0%)	2 (1.8%)	2 (2.2%)	**ns** (p=0.82)
Hot food/drink	2 (1.0%)	1 (0.9%)	1 (1.1%)	**ns** (p=0.87)
Cold food/drink	4 (2.0%)	2 (1.8%)	2 (2.2%)	**ns** (p=0.82)
Alcohol	7 (3.5%)	4 (3.6%)	3 (3.4%)	**ns** (p=0.94)
Chocolate	5 (2.5%)	5 (4.5%)	0 (0%)	* (p=0.04)
Cheese	4 (2.0%)	3 (2.7%)	1 (1.1%)	**ns** (p=0.43)
Relieving factors				
Analgesics	105 (52.2%)	54 (48.2%)	51 (57.3%)	**ns** (p=0.20)
Rest	85 (42.3%)	48 (42.9%)	37 (41.6%)	**ns** (p=0.86)
Pressure	77 (38.3%)	38 (33.9%)	39 (43.8%)	**ns** (p=0.15)
Heat	50 (24.9%)	29 (25.9%)	21 (23.6%)	**ns** (p=0.71)
Alcohol	11 (5.5%)	7 (6.3%)	4 (4.5%)	**ns** (p=0.59)
Chewing	8 (4.0%)	6 (5.4%)	2 (2.2%)	**ns** (p=0.26)

8.3.3 <u>TMD signs and symptoms, summary of responders</u>. (table 59a,59b)

There are no significant differences in TMJ symptoms or character of pain described apart (table 59a) or the reporting of other chronic recurrent pains (table 59b). Frequency, diurnal variation, bruxism and occlusal habits were not significantly different between categories (table 59c). TMJ signs recorded at initial examination were also comparable and non significant (table 59d).

Table 59d: Frequency, diurnal variation, bruxism and occlusal discomfort in TMJ pain

Frequency of TMJ pain	All groups (n=201)	Responders (n=112)	Non Responders (n=89)	significance
Always	78 (38.8%)	49 (43.8%)	29 (32.6%)	**ns** (p=0.081)
Often	60 (29.9%)	38 (33.9%)	22 (24.7%)	
Occasionally	13 (6.5%)	8 (7.1%)	5 (5.6%)	
Always dull, occasionally sharp	46 (21.6%)	15 (13.4%)	31 (34.9%)	
Often dull, occasionally sharp	4 (2.0%)	2 (1.8%)	2 (2.2%)	
Length of bouts				
Constant	150 (74.6%)	87 (77.7%)	63 (73.6%)	**ns** (p=0.521)
Weeks	3 (1.5%)	2 (1.8%)	1 (1.1%)	
Days	22 (10.9%)	12 (10.7%)	10 (11.2%)	
Hours	19 (9.5%)	7 (6.3%)	12 (13.5%)	
Minutes	7 (3.5%)	4 (3.6%)	3 (3.4%)	
Frequency of bouts				
Constant	150 (74.6%)	87 (77.7%)	63 (70.8%)	**ns** (p=0.470)
Daily	36 (17.9%)	18 (16.1%)	18 (20.2%)	
Weekly	14 (7.0%)	6 (5.4%)	8 (9.0%)	
Monthly	1 (0.5%)	1 (0.9%)	0 (0%)	
Pain free intervals				
None	150 (74.6%)	87 (77.7%)	63 (70.8%)	**ns** (p=0.341)
Weeks	11 (5.5%)	4 (3.6%)	7 (7.9%)	
Days	40 (19.9%)	21 (18.8%)	19 (21.3%)	

Diurnal variation in TMJ pain				
Worse in the morning	96 (47.8%)	60 (53.6%)	36 (40.4%)	**ns** (p=0.064)
Worse in the evening	54 (26.9%)	28 (25.0%)	26 (29.2%)	**ns** (p=0.503)
Altered sleep patterns				
Prevention of sleep	93 (46.3%)	50 (44.6%)	43 (48.3%)	**ns** (p=0.604)
Disturbance of sleep	94 (46.8%)	51 (45.5%)	43 (48.3%)	**ns** (p=0.695)
Sleep alterations				
No problems	83 (41.3%)	43 (38.4%)	40 (44.9%)	**ns** (p=0.482)
Cannot get to sleep	25 (12.4%)	13 (11.6%)	12 (13.5%)	
Disturbed sleep	43 (21.4%)	28 (25.0%)	15 (16.9%)	
Early morning waking	8 (4.0%)	5 (4.5%)	3 (3.4%)	
Cannot get to sleep and disturbed sleep	19 (9.5%)	9 (8.0%)	10 (11.2%)	
Cannot get to sleep and early waking	2 (1.0%)	0 (0%)	2 (2.2%)	
Disturbed sleep and early waking	10 (5.0%)	7 (6.3%)	3 (3.4%)	
Cannot get to sleep, disturbed sleep and early morning waking	11 (5.5%)	7 (6.3%)	4 (4.5%)	
Bruxism and occlusal comfort				
Nocturnal bruxism habit	39 (19.4%)	23 (20.5%)	16 (18.0%)	**ns** (p=0.649)
Sensation of disturbed occlusal comfort	110 (54.7%)	68 (60.7%)	42 (47.2%)	**ns** (p=0.056)

Table 59e: TMJ signs

TMJ signs	All groups (n=201)	Responders (n=112)	Non Responders (n=89)	Significance
TMJ pain				
Tenderness	201(100%)	112 (100%)	89 (100%)	-
Right	135(67.2%)	75 (67.0%)	60 (67.4%)	ns (p=0.946)
Left	137(68.2%)	76 (67.9%)	61 (68.5%)	ns (p=0.918)
Opening click				
Right	40 (19.9%)	23 (20.5%)	17 (19.1%)	ns (p=0.800)
Left	55 (27.4%)	25 (22.3%)	30 (33.7%)	ns (p=0.072)
Closing click				
Right	16 (8.0%)	10 (8.9%)	6 (6.7%)	ns (p=0.569)
Left	26 (12.9%)	10 (8.9%)	16 (18.0%)	ns (p=0.058)
Deviation on mouth opening				
Right	5 (2.5%)	1 (0.9%)	4 (4.5%)	ns (p=0.103)
Left	8 (4.0%)	2 (1.8%)	6 (6.7%)	ns (p=0.074)
Sticking				
Right	4 (2.0%)	3 (2.7%)	1 (1.1%)	ns (p=0.433)
Left	5 (2.5%)	3 (2.7%)	2 (2.2%)	ns (p=0.845)

Recorded at baseline assessment	All groups (n=201)	Responders (n=112)	Non Responders (n=89)	Significance
Occlusion Angles classification				
Class I	81 (40.3%)	47 (42.0%)	34 (38.2%)	ns (p=0.411)
Class II division i	78 (38.8%)	44 (39.3%)	34 (38.2%)	
Class II division ii	40 (19.9%)	19 (17.0%)	21 (23.6%)	
Class III	2 (1.0%)	2 (1.8%)	0 (0%)	
Overjet > 6mm	11 (5.5%)	4 (3.6%)	7 (7.9%)	ns (p=0.184)
Buccal mucosa				
Ridging	109 (54.2%)	59 (52.7%)	50 (56.2%)	ns (p=0.621)
Frictional keratosis	10 (5.0%)	6 (5.4%)	4 (4.5%)	ns (p=0.780)
Abrasion	6 (3.0%)	2 (1.8%)	4 (4.5%)	ns (p=0.262)
Lingual mucosa				
Ridging (scalopped margin)	24 (11.9%)	14 (12.5%)	10 (11.2%)	ns (p=0.784)
Missing posterior teeth				
Greater than five	24 (11.9%)	17 (15.2%)	7 (7.9%)	ns (p=0.112)
Greater than six	11 (5.5%)	8 (7.1%)	3 (3.4%)	ns (p=0.243)
Missing wisdom teeth				
None	70 (34.8%)	41 (36.6%)	29 (32.6%)	ns (p=0.794)
One	13 (6.5%)	9 (8.0%)	4 (4.5%)	
Two	32 (15.9%)	17 (15.2%)	15 (16.9%)	
Three	19 (9.5%)	10 (8.9%)	9 (10.1%)	
Four	67 (33.3%)	35 (31.3%)	32 (36.0%)	
Missing maxillary canine tooth	6 (3.0%)	2 (1.8%)	4 (4.5%)	ns (p=0.432)

8.3.4 Responders and non responders to therapy (>50% improvement in pain)

Treatment responders and non responders were categorised using the primary outcome measure of >50% pain improvement at the end of the three months treatment phase, from the clinical visual analogue scale, using the rigorous imputation analysis (n=250) (,table 56).Demographic, initial self reported pain questionnaires, clinical history and examination findings were analysed to assess differences in those responding positively to therapy.

Table 60: Greater than 50% improvement at three months VAS (clinical)

>50% improvement in VAS (clinical) at 3/12	SSRI	Placebo	Splint	SSRI and Splint	Total
Non Responder	40 (63.5%)	50 (79.3%)	47 (75.8%)	45 (72.6%)	182
Responder	23 (36.5%)	13 (20.6%)	15 (24.2%)	17 (27.4%)	68
Total	63	63	62	62	250

8.3.5 Demographics, summary of responders (table 57)

Between category comparisons suggest no significant difference in age, gender, employment, socioeconomic status or pain duration.

Examining the referral source, the majority of all referrals were from GDP's , responders 63/68 (92.6%) and non responders 167/182 (91.8%).However, a higher percentage of non responders were tertiary referrals from Consultant specialists 13/182 (7.1%) as opposed to 1/68 (1.5%), p=0.023.

Marital status also varied. In both categories, the majority of patients were single, although slightly higher in responders 45/68 (66.2%) than non responders 102/182 (56%).A similar proportion of patients were married 22/68 (32.3%) in responders and 67/182 (36.8%) in non responders but a significantly higher proportion of patients were divorced 11/182 (6%) in the non responders compared to zero in the responders, p=0.035.

8.3.6 Self-report pain questionnaire, summary of responders (table 58)

The table illustrates there was no significant difference in initial scores of patient's perspective of pain and impact on daily life. The attitude and actions of significant family or friends suggests a punishing response was just significantly higher amongst non responders p=0.036. Frequency of participation in social activities again seemed to be higher amongst non responders p=0.036.

8.3.7 TMD signs and symptoms, summary of responders. (table 59,60)

There are no significant differences in TMJ symptoms or character of pain described (table 59) or the reporting of other chronic recurrent pains (table 60).

8.3.8 TMD description, summary of responders. (table 61,62,63)

Onset, exacerbation or relief of pain (table 61) only suggests a slight increase in the amount of analgesia usually taken to relieve pain in non responders 103/182 (56.6%) compared to 29/68 (42.6%) in responders to therapy p=0.049.
Frequency, diurnal variation, bruxism and occlusal habits were not significantly different between categories (table 62). TMJ signs recorded at initial examination were also comparable and non significant (table 63).

Table 61:

Demographic details for responders and non responders to treatment (N=250)

Recorded at baseline assessment	All groups (n=250)	**Responders** (n=68)	**Nonresponders** (n=182)	Significance
Age (in years) Mean (+/- SD) Range	32.3 (9.58) (16-55)	32.9 (10.49) (16-55)	32.1 (9.23) (16-54)	**ns** (p=0.560)
Duration of pain (in yrs) Mean (+/- SD) Range	3.30 (4.49) (0.25-32.0)	3.08 (4.11) (0.25-32.0)	3.38 (4.64) (0.25-32.0)	**ns** (p=0.639)
Gender M: F	59: 191 23.6%:76.4%	16: 52 23.5%:76.5%	43: 139 23.6%:76.4%	**ns** (p=0.987)
Referral source GDP GP Specialist	230 (92%) 6 (2.4%) 14 (5.6%)	63 (92.6%) 4 (5.9%) 1 (1.5%)	167(91.8%) 2 (1.1%) 13 (7.1%)	* (p=0.023)
Employment status Employed Unemployed Student Retired (medical) House wife	167 (66.8%) 19 (7.6%) 39 (15.6%) 1 (0.4%) 24 (9.6%)	43 (63.2%) 10 (14.7%) 10 (14.7%) 0 (0%) 5 (7.4%)	124 (68.1%) 9 (4.9%) 29 (15.9%) 1 (0.5%) 19 (10.4%)	**ns** (p=0.121)
Socio-economic status Professional I Intermmediate IIi Skilled non-manual IIii Skilled manual III Semi skilled IV Unskilled V Unemployed, house wife, student, retired VI	11 (4.4%) 78 (31.2%) 66 (26.4%) 8 (3.2%) 5 (2.0%) 1 (0.4%) 81 (32.4%)	2 (2.9%) 23 (33.8%) 18 (26.5%) 0 (0%) 0 (0%) 0 (0%) 25 (36.8%)	9 (4.9%) 55 (30.2%) 48 (26.4%) 8 (4.4%) 5 (2.7%) 1 (0.5%) 56 (30.7%)	**ns** (p=0.437)
Marital status Single Married Seperated Divorced Widowed	147 (58.8%) 89 (35.6%) 2 (0.8%) 11 (4.4%) 1 (0.4%)	45 (66.2%) 22 (32.3%) 1 (1.5%) 0 (0%) 0 (0%)	102 (56.0%) 67 (36.8%) 1 (0.5%) 11 (6.0%) 1 (0.5%)	* p=0.035

Significance test, Chi-squared (Independent samples t-test for age and duration).

Table 62: Self -Report Pain Questionnaires at baseline (Responders and Non responders)

MPI	(n=250) All groups	(n=68) Responders	(n=182) Non responders	Significance
Patients perspective of pain and impact on daily life				
MPI - Severity	3.00 (1.92,4.00)	2.60 (1.66, 4.00)	3.00 (2.00, 4.00)	ns (p=0.299)
MPI - Interference	1.45 (0.65,2.88)	1.39 (0.73, 3.02)	1.45 (0.60, 2.82)	ns (p=0.895)
MPI – Life control	3.25 (2.31,4.00)	3.25 (2.56, 4.00)	3.25 (2.25, 4.25)	ns (p=0.876)
MPI – Affective distress	3.33 (2.33,4.30)	3.00 (2.08, 4.23)	3.33 (2.60, 4.30)	ns (p=0.277)
Response of significant other person to patient				
MPI – Support response	3.33 (2.30,4.66)	4.00 (2.66, 4.66)	3.00 (2.00, 4.47)	ns (p=0.233)
MPI – Punishing response	1.00 (0,2.06)	0.58 (0.00, 1.75)	1.00 (0.25, 2.50)	* **(p=0.036)**
MPI – Solicitous response	2.66 (1.50,3.87)	2.50 (1.04, 3.83)	2.66 (1.60, 4.00)	ns (p=0.542)
MPI – Distracting response	1.75 (0.75,2.75)	1.75 (0.50,2.75)	1.75 (0.75, 2.81)	ns (p=0.555)
Frequency of participation in common activities				
MPI – Household chores	4.80 (3.60,5.60)	4.80 (3.40, 5.40)	4.80 (3.60, 5.80)	ns (p=0.429)
MPI – Outdoor work	2.00 (1.00,3.00)	2.00 (1.30, 3.30)	1.75 (1.00, 2.80)	ns (p=0.104)
MPI – Activities away from home	3.50 (2.75,4.25)	3.50 (2.50, 4.25)	3.50 (2.75, 4.50)	ns (p=0.476)
MPI – Social activities	3.00 (2.30,4.00)	2.75 (2.25, 3.66)	3.25 (2.32, 4.00)	* **(p=0.036)**
MPI – General activity level	3.38 (2.75,3.91)	3.33 (2.77, 3.79)	3.44 (2.71, 3.98)	ns (p=0.409)
MPQ				
Visual analogue scale (VAS) (range 0-10)	2.90 (1.20,5.45)	2.30 (1.20, 4.60)	3.00 (1.25, 5.65)	ns (p=0.223)
Present pain intensity (PPI) (range 0-5)	2.00 (1.00,2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	ns (p=0.195)
MPQ – total % (range 0-100)	31.0 (20.0,47.0)	29.0 (18.00,40.00)	31.0 (20.5,47.00)	ns (p=0.182)
MPQ– sensory % (range 0-100)	33.0 (21.0,45.0)	31.5(20.25, 42.25)	34.5 (21.00,47.75)	ns (p=0.435)
MPQ – affective % (range 0-100)	17.0 (3.0,42.0)	17.0 (0.0, 42.00)	25.0 (8.00, 42.0)	ns (p=0.097)
BDI				
Composite score (range 0-45)	7.0 (3.00,13.0)	7.0 (2.00, 13.00)	7.0 (3.00, 12.75)	ns (p=0.326)
Kellner				
Illness attitude- total (range 0-30)	8.0 (6.0,11.0)	7.0 (6.00, 10.00)	8.0 (6.00, 12.00)	ns (p=0.336)
Hypochondriacal beliefs (range 0-15)	3.00 (3.00,6.00)	3.00 (3.00,5.75)	3.00 (3.00,6.00)	ns (p=0.870)
Disease phobia (range 0-15)	3.00 (3.00,5.00)	3.00 (3.00,5.00)	3.00 (3.00, 5.75)	ns (p=0.200)

Table 63a: TMJ symptoms

Baseline record prior to treatment	**All groups** (n=250)	**Responders** (n=68)	**NonResponders** (n=182)	Significance
TMJ symptoms				
TMJ pain	250 (100%)	68 (100%)	182 (100%)	-
Muscle pain – Temporalis	65 (26%)	19 (27.9%)	46 (25.3%)	**ns** (p=0.669)
Muscle pain - Masseter	80 (32%)	25 (26.8%)	55 (30.2%)	**ns** (p=0.324)
Clicking	192 (76.8%)	57 (83.8%)	135 (74.2%)	**ns** (p=0.108)
Sticking	76 (30.4%)	18 (26.5%)	58 (31.9%)	**ns** (p=0.409)
Limitation in mouth opening	187 (74.8%)	46 (67.6%)	141 (77.5%)	**ns** (p=0.111)
Ear popping	51 (20.4%)	14 (20.6%)	37 (20.3%)	**ns** (p=0.964)
Ear buzzing	37 (14.8%)	14 (20.6%)	23 (12.6%)	**ns** (p=0.115)
Ear deafness	37 (14.8%)	13 (19.1%)	24 (13.2%)	**ns** (p=0.240)
Ear fullness	62 (24.8%)	15 (22.1%)	47 (25.8%)	**ns** (p=0.540)
Character of TMJ pain				
Dull ache	161 (64.4%)	45 (66.2%)	116 (63.7%)	**ns** (p=0.720)
Discomfort	137 (54.8%)	43 (63.2%)	94 (51.6%)	**ns** (p=0.101)
Sharp	99 (39.6%)	31 (45.6%)	68 (37.4%)	**ns** (p=0.237)
Stabbing	35 (14%)	10 (14.7%)	25 (13.7%)	**ns** (p=0.844)
Throbbing	20 (8%)	5 (7.4%)	15 (8.2%)	**ns** (p=0.818)
Burning	6 (2.4%)	1 (1.5%)	5 (2.7%)	**ns** (p=0.557)
Unilateral	180 (72%)	45 (66.2%)	135 (74.2%)	**ns** (p=0.210)

Table 63b: Other reported chronic pains

Recorded at baseline assessment	(n=250) All groups	(n=68) Responders	(n=182) Non responders	Significance
Recurrent chronic pains				
Headache	61.2% (153)	54.4% (37)	63.7% (116)	**ns** (p=0.178)
Migraine	32.8% (82)	39.7% (27)	30.2% (55)	**ns** (p=0.155)
Neck ache	50.0% (125)	42.6% (29)	52.7% (96)	**ns** (p=0.155)
Back pain	48.4% (121)	41.2% (28)	51.1% (93)	**ns** (p=0.162)
Abdominal pain	29.6% (74)	27.9% (19)	30.2% (55)	**ns** (p=0.725)
Pruritus	22.0% (55)	14.7% (10)	24.7% (45)	**ns** (p=0.089)
Chest pain	15.6% (39)	16.2% (11)	15.4% (28)	**ns** (p=0.878)

Table 63c: Onset ,exacerbation and relief of TMJ pain

Base line record	(n=250) All groups	(n=68) Responders	(n=182) Non Responders	Significance
Precipitating factors				
Dental	26.4% (66)	30.9% (21)	24.7% (45)	ns (p=0.326)
Physical trauma	15.6% (39)	11.8% (8)	17.0% (31)	ns (p=0.307)
Emotional trauma	2.8% (7)	19.1% (13)	25.8% (47)	ns (p=0.269)
Infection	24.0% (60)	1.5% (1)	3.3% (1)	ns (p=0.436)
None	26.8% (67)	23.5% (16)	28.0% (51)	ns (p=0.475)
Provoking factors				
Chewing	76.8% (192)	82.4% (56)	74.7% (136)	ns (p=0.204)
Yawning	76.4% (191)	82.4% (56)	74.2% (135)	ns (p=0.175)
Biting	65.6% (164)	66.2% (45)	65.4% (119)	ns (p=0.907)
Emotional tension	53.6% (134)	57.4% (39)	52.2% (95)	ns (p=0.467)
Talking	31.6% (79)	29.4% (20)	32.4% (59)	ns (p=0.649)
Cold weather	28.8% (72)	30.9% (21)	28.0% (51)	ns (p=0.657)
Hot weather	2.4% (6)	2.7% (5)	1.5% (1)	ns (p=0.557)
Hot food/drink	1.6% (4)	0% (0)	2.2% (4)	ns (p=0.218)
Cold food/drink	2.4% (6)	1.5% (1)	2.7% (5)	ns (p=0.557)
Alcohol	3.2% (8)	2.9% (2)	3.3% (6)	ns (p=0.887)
Chocolate	2.0% (5)	4.4% (3)	1.1% (2)	ns (p=0.096)
Cheese	1.6% (4)	2.9% (2)	1.1% (2)	ns (p=0.302)
Relieving factors				
Analgesics	52.8% (132)	42.6% (29)	56.6% (103)	* p=0.049
Rest	44.0% (110)	52.9% (36)	40.7% (74)	ns p=0.082
Pressure	38.4% (96)	42.6% (29)	36.8% (67)	ns p=0.339
Heat	24.0% (60)	25.0% (17)	23.6% (43)	ns p=0.821
Alcohol	6.4% (16)	8.8% (6)	5.5% (10)	ns p=0.339
Chewing	3.2% (8)	2.9% (2)	3.3% (6)	ns p=0.887

Table 63d: Frequency, diurnal variation, bruxism and occlusal discomfort in TMJ pain

Frequency of TMJ pain	All groups (n=250)	Responders (n=68)	Non Responders (n=182)	significance
Always	151 (60.4%)	25 (36.8%)	72 (39.6%)	**ns** (p=0.763)
Often	83 (33.2%)	18 (26.5%)	59 (32.4%)	
Occasionally	16 (6.4%)	4 (5.9%)	12 (6.6%)	
Always dull, occasionally sharp	54 (21.6%)	19 (28.0%)	35 (19.2%)	
Often dull, occasionally sharp	6 (2.4%)	2 (2.9%)	4 (2.2%)	
Length of bouts				
Constant	185 (74.0%)	51 (75.0%)	134 (73.6%)	**ns** (p=0.996)
Weeks	5 (2.0%)	1 (1.5%)	4 (2.2%)	
Days	31 (12.4%)	8 (11.8%)	23 (12.6%)	
Hours	22 (8.8%)	6 (8.8%)	16 (8.8%)	
Minutes	7 (2.8%)	2 (2.9%)	5 (2.7%)	
Frequency of bouts				
Constant	185 (74.0%)	51 (75.0%)	134 (73.6%)	**ns** (p=0.931)
Daily	43 (17.2%)	12 (17.6%)	31 (17.0%)	
Weekly	19 (7.6%)	4 (5.9%)	15 (8.2%)	
Monthly	3 (1.2%)	1 (1.5%)	2 (1.1%)	
Pain free intervals				
None	185 (74.0%)	51 (75.0%)	134 (73.6%)	**ns** (p=0.883)
Weeks	14 (5.6%)	3 (4.4%)	11 (6.0%)	
Days	51 (20.4%)	14 (20.6%)	37 (20.3%)	

Diurnal variation in TMJ pain				
Worse in the morning	113 (45.2%)	33 (48.5%)	80 (44.0%)	**ns** (p=0.518)
Worse in the evening	70 (28.0%)	20 (29.4%)	50 (27.5%)	**ns** (p=0.761)
Altered sleep patterns				
Prevention of sleep	113 (45.2%)	35 (51.5%)	78 (42.9%)	**ns** (p=0.223)
Disturbance of sleep	117 (46.8%)	32 (47.1%)	85 (46.7%)	**ns** (p=0.960)
Sleep alterations				
No problems	98 (39.4%)	26 (38.2%)	72 (39.6%)	**ns** (p=0.422)
Cannot get to sleep	33 (13.2%)	12 (17.6%)	22 (12.1%)	
Disturbed sleep	58 (23.2%)	16 (23.5%)	42 (23.1%)	
Early morning waking	8 (3.2%)	0 (0%)	8 (4.4%)	
Cannot get to sleep and disturbed sleep	22 (8.8%)	5 (7.4%)	17 (9.3%)	
Cannot get to sleep and early waking	3 (1.2%)	1 (1.5%)	2 (1.1%)	
Disturbed sleep and early waking	13 (5.2%)	2 (2.9%)	11 (6.0%)	
Cannot get to sleep, disturbed sleep and early morning waking	14 (5.6%)	6 (8.8%)	8 (4.4%)	
Bruxism and occlusal comfort				
Nocturnal bruxism habit	49 (19.6%)	10 (14.7%)	39 (21.4%)	**ns** (p=0.233)
Sensation of disturbed occlusal comfort	133 (53.2%)	36 (52.9%)	97 (53.3%)	**ns** (p=0.960)

Table 63e: TMJ signs

TMJ signs	All groups	Responders	Non Responders	Significance
TMJ pain				
Tenderness	250 (100%)	68 (100%)	182 (100%)	-
Right	162(64.8%)	44 (64.7%)	118 (64.8%)	ns (p=0.985)
Left	173(69.2%)	48 (70.6%)	125 (68.7%)	ns (p=0.771)
Opening click				
Right	51 (20.4%)	15 (22.1%)	36 (19.8%)	ns (p=0.691)
Left	69 (27.6%)	19 (27.9%)	50 (27.5%)	ns (p=0.941)
Closing click				
Right	24(9.6%)	6 (8.8%)	18 (9.9%)	ns (p=0.799)
Left	36(14.4%)	8 (11.8%)	28 (15.4%)	ns (p=0.468)
Deviation on mouth opening				
Right	10(4%)	1 (1.5%)	9 (4.9%)	ns (p=0.212)
Left	10(4%)	1 (1.5%)	9 (4.9%)	ns (p=0.212)
Sticking				
Right	7(2.8%)	1 (1.5%)	6 (3.3%)	ns (p=0.436)
Left	6(2.4%)	1 (1.5%)	5 (2.7%)	ns (p=0.557)

Recorded at baseline assessment	n=68 Responders	n=182 Non Responders	Significance
Occlusion			
Angles classification			
Class I	25 (36.8%)	73 (40.1%)	ns (p=0.365)
Class II division i	24 (35.3%)	71 (39.0%)	
Class II division ii	17 (25.0%)	37 (20.3%)	
Class III	2 (2.9%)	1 (0.5%)	
Overjet > 6mm	4 (5.9%)	9 (4.9%)	ns (p=0.766)
Buccal mucosa			
Ridging	37 (54.4%)	95 (52.2%)	ns (p=0.537)
Frictional keratosis	2 (2.9%)	13 (7.1%)	ns (p=0.213)
Abrasion	2 (2.9%)	5 (2.7%)	ns (p=0.934)
Lingual mucosa			
Ridging (scalopped margin)	7 (10.3%)	24 (13.2%)	ns (p=0.537)
Missing posterior teeth			
Greater than five	10 (14.7%)	15 (8.2%)	ns (p=0.130)
Greater than six	4 (5.9%)	8 (4.4%)	ns (p=0.625)
Missing wisdom teeth			
None	21 (30.9%)	71 (39.0%)	ns (p=0.629)
One	5 (7.4%)	10 (5.5%)	
Two	9 (13.2%)	30 (16.5%)	
Three	7 (10.3%)	15 (8.2%)	
Four	26 (38.2%)	56 (30.8%)	
Missing maxillary canine tooth	3 (4.4%)	4 (2.2%)	ns (p=0.565)

VIII DISCUSSION

8.4 Subgroup analysis

Hypothesis (6a) , (6b), (6c)

(6a) A significant and measurable improvement in pain is only seen in those patients without depression

(6b) A significant and measurable improvement in pain measures are only seen in those patients with initially high pain scores

(6c) Clinical and pain history characteristics at baseline separate the treatment responders from the non responders

Subgroup analysis allows examination of treatment effect and observation of qualitative interaction in subjects with particular characteristics; an important clinical consideration when caring for individual patients, (Peduzzi,2002). However, caution should be taken in interpretation due to the poor reliability of subgroup analysis arising from multiplicity, as previously discussed, and small sample sizes compared to the entire group analysis. Results of subgroup analysis are therefore not definitive but exploratory for formulating further research hypotheses, (Peduzzi, 2002).

8.4.1 Depressed and non depressed patients

Depression warranted investigation as it is an important component in the management of pain conditions, (Arnow et al, 2006).

TMJ pain causing disturbance and prevention of sleep was significantly higher amongst the depressed category $p<0.001$. This finding concurs with the concept of alteration in sleep patterns and depression, (Taylor et al, 2005, Rosen et al, 2006, Lam, 2006). It is now well recognised that depression is a consequence of chronic

pain, (Arnow et al, 2006). However, speculation as to whether depression and problematic sleep lead to the TMJ symptoms or whether the TMJ symptoms lead to sleep deprivation and depression is an interesting concept. This comorbidity of reported sleep disturbance and psychological distress in patients with chronic TMD has also been shown by others (Yatani et al, 2002, Lavigne, 2006).
Interestingly, chronic sleep restriction has recently been shown to cause a gradual and prolonged desensitisation of the (5-HT)1A receptor system, suggesting a link between chronic sleep loss and sensitivity disorders associated with altered serotonergic neurotransmission, (Roman et al, 2005).

An interesting finding was the patient's association of emotional factors to onset of TMJ pain $p=0.049$ and provocation of TMJ pain $p<0.001$, highest in depressed groups. This perhaps suggests either a greater awareness of the psychological aspects of pain or an increased psychological component to the pain in these individuals. Other recurrent chronic pains: headache $p=0.021$, neck ache $p=0.007$, backache $p=0.049$ and abdominal pain $p=0.01$ are higher in the depressed group at baseline. Despite significant reduction in reported pains during the course of therapy this was more pronounced in the non depressed groups; headaches $p<0.001$, abdominal pain $p<0.001$, neck ache $p<0.001$ and backache $p=0.01$. Risk factors for depression were related to temporal muscle pain at baseline OR=2.67 (CI 1.45,4.93)$p<0.001$; abdominal pain OR =2.06 (CI 1.33,3.76) $p<0.018$ and dental pain OR=7.18 (CI 1.32,39.05)$p<0.023$. With regards to temporal muscle pain, previous studies have similarly reported an association between myalgic pain and depression, (Kight,Gatchel and Wesley,1999). As might be expected the self report pain questionnaires revealed an increased risk of depression with decreased MPI life

control OR=0.45; increased Kellner illness attitude (hypochondriacal beliefs and disease phobia) OR=1.24 and MPI punishing response of others OR=1.50. Decreased depression was observed in increased MPI activities away from home OR=0.68.

8.4.1.1 Analysing reduction in pain severity (Tables 41-48)

Before making any assumptions regarding the effect of depression on therapeutic outcome it should be noted that statistically there was no clearly significant difference between groups. Frequency improvement again appeared more successful in the non-depressed category for groups 1,2 and 3 $p<0.001$ compared to $p<0.05$. However, although interference improved more significantly in non depressed categories in groups 2 ($p<0.005$) and 3 ($p<0.05$), both groups improved equally in groups 1 and 4 ($p<0.001$). PPI again improved almost equally in group 4, group 3 non depressed improved more significantly $p<0.001$ compared to depressed $p=0.045$ whilst group 1 the observation was reversed and the depressed group improved more significantly p,0.001 than the non depressed.

MPI perspective of pain revealed equal improvement in severity p,0.001 and interference $p<0.005$ in both depressed and non depressed categories, whereas life control $p<0.05$ and effective distress $p<0.005$ improved to a lesser extent in the non depressed categories. The reverse was once again seen in groups 2 and 3 where more significant improvements were seen in the non depressed groups. MPQ scores significantly improved amongst the non depressed group VAS total % ($p<0.001$) and sensory % ($p<0.005$) but to a lesser extent in depressed ,VAS ($p<0.05$) total% ($p<0.005$) whilst affective % was successfully improved ($p<0.005$) and PPI ($P<0.001$). Intra group analysis showed improvement in PPI amongst the depressed

in groups 1 and 2 ($p<0.05$) but non depressed in groups 3 and 4 ($p<0.05$). Only non depressed patients appear to improve significantly in group 3 PPI $p<0.05$ MPQ sensory % and affective % $p<0.05$ and total % $p<0.05$.

Broadly, results would imply that non depressed patients respond more favourably to physical therapy whilst the depressed react to medical therapy but this was not a significant finding. Depression in relation to medical therapeutic intervention might warrant further investigation with additional use of more sensitive psychological rating scales.

The logistic regression analysis suggesting other concurrent chronic pains, a myalgic and dental TMJ pain component, social environmental interaction with others, altered sleep patterns, emotional factors and the level of life control over pain do have a significant effect on the level of depression in these individuals with TMJ pain.

Depressed patients were slightly older with a mean age of 34 years (18-55) compared to the non depressed group 31years (16-53) $p<0.05$. The primary outcome measure of the VAS did appear to show a significant improvement in the non depressed group $p<0.001$ compared with improvement in the depressed group $p<0.05$. However, this difference was not significant . For the secondary outcome measures; pain improvement, responders and frequency again appeared more successful in the non depressed group.

For PPI; an interesting pattern emerges where depressed patients report greater improvement in scores in group1 taking antidepressants, whilst nondepressed patients report greater improvement in scores in group 3 the physical therapy group. However, findings are still non-significant between groups.

Interference with life improved significantly in the non depressed groups but in depressed groups was more pronounced in those who received medication, group1 and group 4. Again, intergroup significance was not achieved.

8.4.2 Responders and non responders to therapy

Greater than 50% improvement in pain, taken as a conservative measure of treatment response, did not reveal any remarkable differences in the demographic and initial baseline recordings. There was no significant difference in age, gender, employment, socioeconomic status or pain duration. A higher percentage of non responders were tertiary referrals from consultant specialists 131/161 (7.1%) p=0.023 which could imply such referrals relate to pain not of longer duration but of a more complex, intractable nature. In relation to marital status there was a higher number of divorcees 11/182 (6%) in the non responders compared to zero in the responders p=0.035 which, one could speculate, might relate to increased levels of previous marital conflict and distress.

Self-report pain questionnaires indicate no difference in initial scores for patient's perspective of pain and impact on daily life. However, the attitude and action of significant family or friends suggest a punishing response was significantly higher amongst non responders p=0.036. One could envisage a negative and unkind response from others could impact on the individuals self esteem. A lack of encouragement and negativity from others might affect their capability in responding to therapy since previous studies suggest a solicitous response by others can be beneficial to pain patients,(Newton-John,2003). Increased frequency of participation in social activities seemed higher amongst non responders p=0.036, in contrast to the finding that increased social activity seemed to reduce the level of

depression. One could hypothesis, that aggravating factors for the pain might therefore relate to stressful social situations, noise, fatigue and alcohol consumption in certain individuals.

The amount of analgesia consumed at baseline was also higher amongst non responders 103/182 (56.6%) compared to 29/68 (42.6%) p=0.049. This may indicate a range of factors which might include a lower pain threshold requiring more frequent medication, an inflammatory element to the pain, more frequent temporal headaches or even an alteration in pain and biochemical receptor response from increased analgesic consumption.

Greater than 25% improvement in pain, did not reveal any differences in age, gender, referral source, pain duration, marital, employment or socioeconomic status. The frequency of participation in social activities was again higher amongst non responders, p=0.030 for completers analysis and p=0.011 for ITT analysis.

8.4. 3 Low and high initial pain scores

There was no discernable difference in the demographic baseline recordings. In relation to other pains there was a significant reduction in headaches in the low compared to the high pain category (p=0.008) and an observable yet not significant reduction in neckache and abdominal pain. VAS reduction was observed in both high and low pain categories $p<0.001$ as reflected in groups 2 and 4. In group1 the high category showed significant reduction $p<0.001$, low category $p<0.005$. Conversely, in group 3 it was the low group which showed more significant reduction $p<0.005$ compared to the high group $p<0.05$. Interference although significantly reduced amongst high and low initial pain categories, was more

significantly reduced in intra group analysis within low categories, particularly groups 2, 3 and 4.

MPI patient's perspective of pain, significantly improved in both pain categories but to a greater extent in high pain scores $p<0.001$. This pattern was observed in group1 but in group 2 and 3 severity improved in both groups but interference and life control only improved in low scorers.

Amongst all groups MPQ: VAS, PPI and total% decreased significantly in the low compared to high categories $p<0.001$ compared to $p=0.012$, $p=0.004$ and $p<0.001$ respectively. A similar trend was observed in group 3 although this was again reversed in group 1 a more favourable outcome in the high category.

BDI decreased significantly in the low category $p=0.001$ amongst all groups which was mirrored by group 3 ($p=0.025$).

Observable findings might lead one to suppose that low pain categories responded favourably to physical therapy whilst high pain categories appeared to respond to medical therapy but such clear cut theory is not substantiated by statistical intergroup analysis which revealed no significant difference between groups for any pain rating scores.

These patients differed slightly in their employment $p<0.005$, socioeconomic $p<0.05$ and marital status $p<0.005$. There was significantly less improvement in primary and secondary outcome measures amongst high pain score patients but once again this was not statistically significant between treatment groups.

In the next chapter maintenance and adherence to therapy are examined together with an analysis of the follow-up data.

9.0 MAINTENANCE AND WITHDRAWAL OF THERAPY AND POST TREATMENT FOLLOW UP

9.1 MAINTENANCE AND WITHDRAWAL OF THERAPY, ADHERENCE AND ADVERSE EVENTS.

9.1.1 Maintenance and withdrawal of participants within the study and follow up.

9.1.1.1 Maintenance (Figures 58, 59, 60 and 12)

250 patients were randomised to participate in the study. 49/250 (19.6%) of patients, although allocated to a therapeutic intervention at baseline, did not commence treatment but withdrew before starting the three month study phase. The remaining 201/250 (80.4%) of patients actually commenced treatment.

When feasible, the recommended intention-to treat (ITT) analysis was conducted on all 250 cases. Where this was not possible due to inadequate or unavailable data an imputation analysis, last-score-brought-forward (LSBF) was conducted. An analysis of complete data records, a pragmatic or completers analysis, was also undertaken to provide a sensitivity analysis.

Overall, 165/201 (82%) of patients who actually commenced treatment successfully completed treatment, constituting a withdrawl rate of 36/201 (18%) from the treatment phase. 138/165 (84%) of patients were successfully maintained throughout the post therapy follow-up phase. This was 138/201 (69%) of the patients who initially commenced therapy, which is a withdrawl rate of 63/201 (31%).

No one group appeared to have a higher erosive rate than another. Between the four therapeutic interventions, there was no significant difference between the numbers who were maintained within the treatment and follow-up phase $\chi^2=0.34$ (3) $p=0.95$.

9.1.1.2 Withdrawal (Tables 64,65 and Figure 61)

The time and reason for withdrawal from the study were recorded. Results were analysed to determine any variability between the different therapeutic interventions

9.1.1.3 Time of withdrawal (Table 64)

Time scale of withdrawal was recorded for each group participant. Pearson Chi squared test revealed no significant difference between the four groups at any of the time points for numbers leaving treatment or indeed for those completing treatment and follow-up.

9.1.1.4 Reasons for withdrawal (Table 65)

Reasons for withdrawal were not significantly different between the four groups, apart from the reasons associated specifically with the therapy provided. The term 'splint and run' was applied to patients who, after attending the appointment for the fitting of their occlusal appliance, took their newly acquired item home but did not return for further appointments. Amongst the four groups this was a significant overall reason for withdrawal, $p<0.001$. It totalled eleven patients, one in group 4 but a significantly increased frequency of 10 patients in group 3, OR=11.7(CI 1.45,94.7) p=0.004 . This is nearly a twelve fold likelihood of disappearing with the occlusal appliance if it were the sole form of treatment as opposed to those receiving combined therapy.
Following randomisation at baseline, eight patients withdrew from treatment because they decided they did not want a splint. This was a significant overall reason between groups for withdrawal p=0.006. Seven patients also withdrew from treatment because they decided against taking medication, although this did not reach overall significance between groups p=0.43
Other reasons for non adherence were not significant between groups but most commonly included : resolution of pain 22/250 (8.8%),no reason given 18/250 (7.2%), time and travel difficulties 14/250 (5.6%) and moved away from locality 8/250 (3.2%). The less frequently reported reasons for non-adherence included: changing to

alternative therapy 4/250 (1.6%), work related problems 4/250 (1.6%) and family health problems 1/250 (0.4%).

With regards to medical therapy reasons for withdrawal at baseline included the disclosure of previously unreported concomitant mental health problems 3/250 (1.2%) or medical history complicating factors which were incompatible with the study inclusion criteria 5/250 (2.0%). During the course of medical therapy two subjects became pregnant and treatment was discontinued 2/250 (0.8%). Both individuals were followed up pre and post partum. During pregnancy TMD resolved in one individual and an occlusal appliance was made for the second individual. Both gave birth to healthy babies with no adverse events.

Five subjects developed side effects to the medical therapy which resulted in discontinuation of treatment, two in group 1, two in group 2 and one in group 4. Three patients discontinued therapy due to gastrointestinal complaints of nausea, vomiting and diarrhoea and one patient developed a rash on the face and torso.

Amongst the four groups the most common reasons for non adherence were in group 1 and 2 'resolution of pain', 8/63 (12.7%) and 6/63 (9.5%) respectively, group 3 'splint and run' 10/62 (16.1%) and group 4 'reason unknown' 5/62 (8.1%).

9.1.2 Adherence (Compliance) (Figure 62) (Tables 66,67)

Adherence previously termed compliance to the therapy was recorded for each group of patients. Adherence measures relied upon patients' self report and additionally, in the case of medication returned bottles and capsule counts. There was no significant difference between the adherence to medication in the three medical therapy groups (1,2 and 4),(table 66).However, there was a significant difference between adherence to splint wear between the two groups (3 and 4) (table 67).This was evident at four

weeks $\chi 2=(1)3.92, p=0.048$ and twelve weeks $\chi 2=(1)4.78, p=0.029$, reflecting a decreased level of adherence in group 3 , occlusal appliance only group.

9.1.3 Adverse events (Side effects)

9.1.3.1 Adverse events to medical therapy (Table 69,70)

The most commonly reported adverse events associated with the fluoxetine groups and not seen at an equivalent incidence among the placebo group were the gastrointestinal symptom of nausea and the nervous system symptoms of insomnia and conversely drowsiness. All adverse events are however non significant between groups apart from the generalised gastrointestinal complaint of nausea. Group 4 the combined splint and SSRI group appeared to have a ten times higher likelihood of nausea compared to the placebo group OR=10.4 (CI 1.2-86) (Table 70).

Overall, there was a significant difference between medical and placebo groups in adverse events reported following the initial treatment phase at four weeks in both group1 OR=2.8 (1.0-7.7) and group 4 OR=2.7 (1.0-7.5) indicating nearly a three fold increase in side effects to medication compared to placebo. However, there was no significant difference in adverse events reported during the subsequent eight and twelve weeks of therapy, (Table 69)

9.1.3.2 Adverse events to physical therapy (Table 68)

Adverse events whilst wearing an occlusal bite guard were recorded throughout treatment. The most commonly reported problems were related to leaving the appliance at home on the day of the appointment. Two patients lost their bite guard and two broke their bite guard. Discomfort in splint wear and poor oral hygiene were not statistically significant between groups.

Figure 58: Maintained within the three month treatment phase.

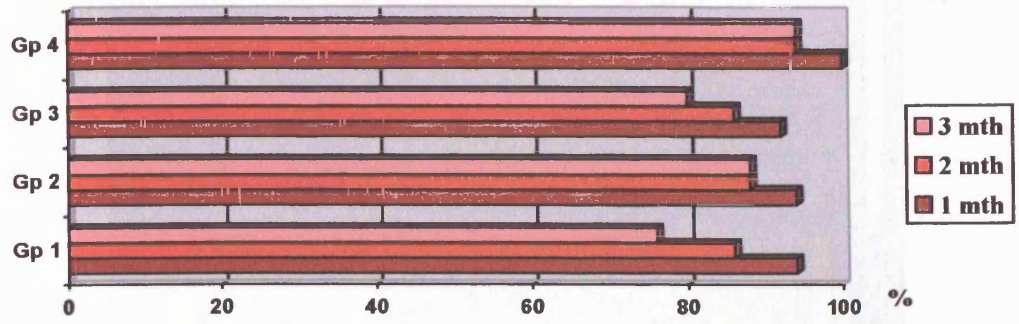


Figure 59: Maintained within follow up, as a percentage of those completing the treatment phase.

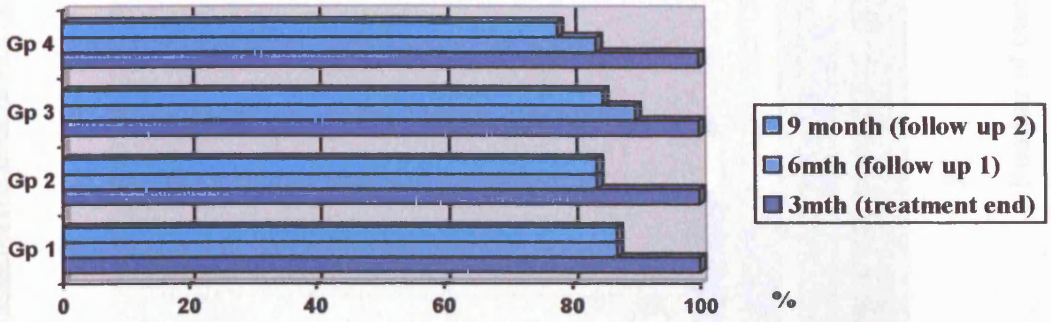


Figure 60: Comparison of completion and withdrawl from the treatment phase and followup phase

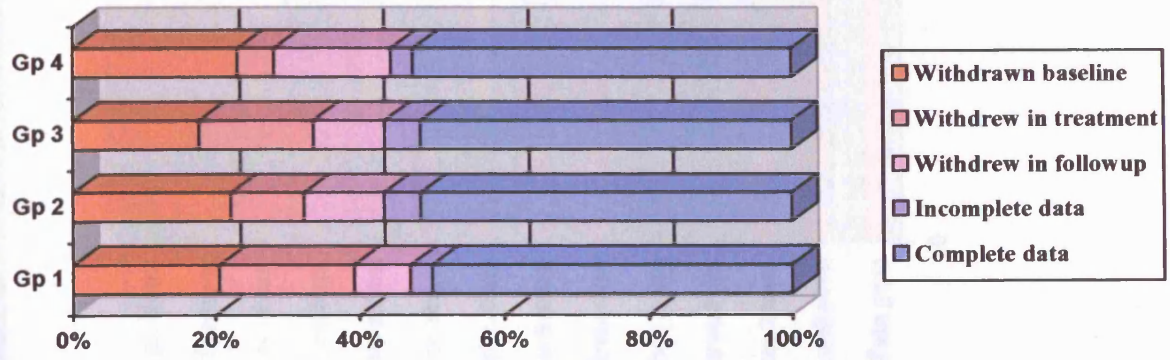


Figure 61 : Reasons for non adherence or withdrawl form treatment and follow-up

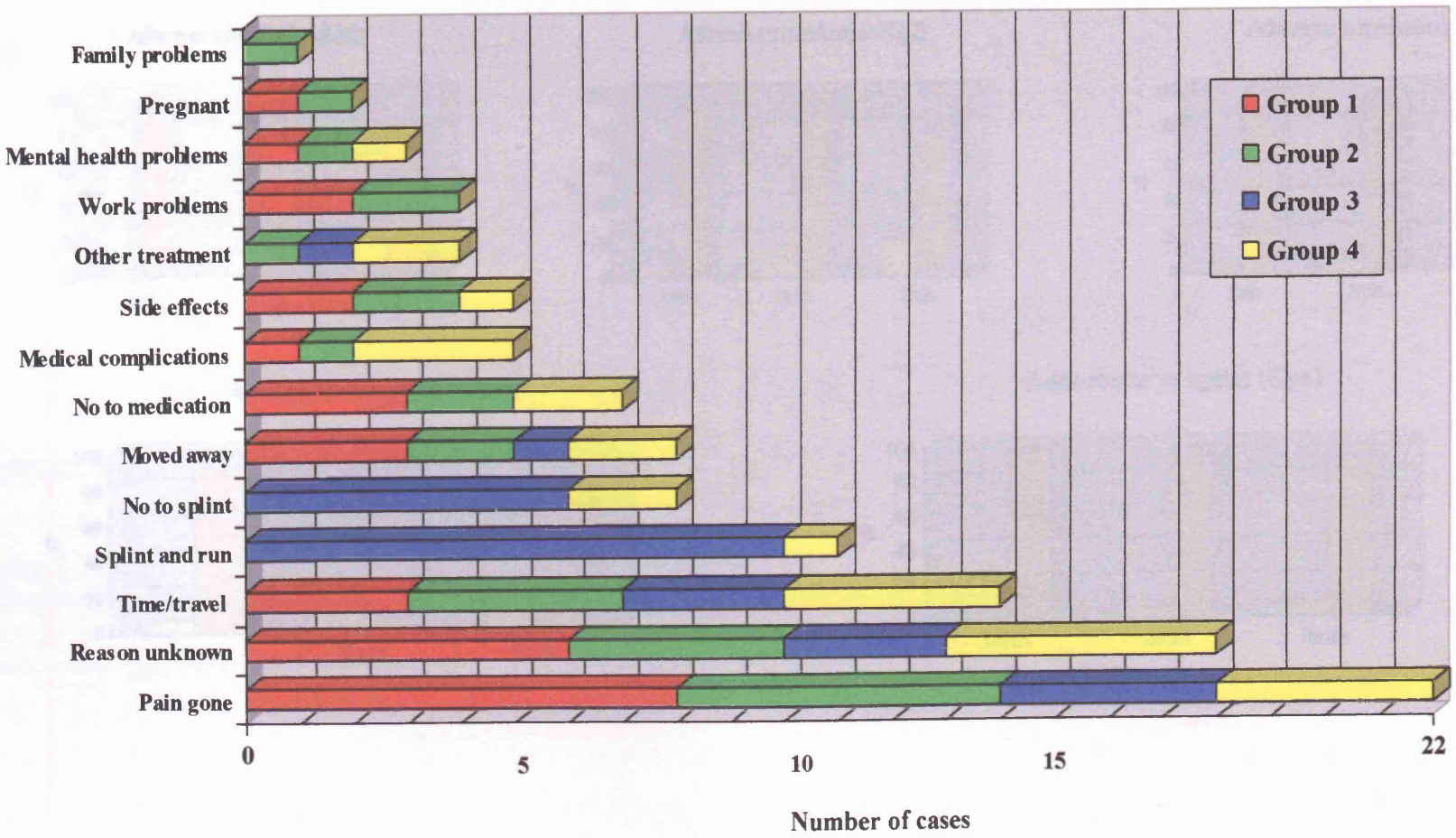


Figure 62: Adherence to allocated therapy

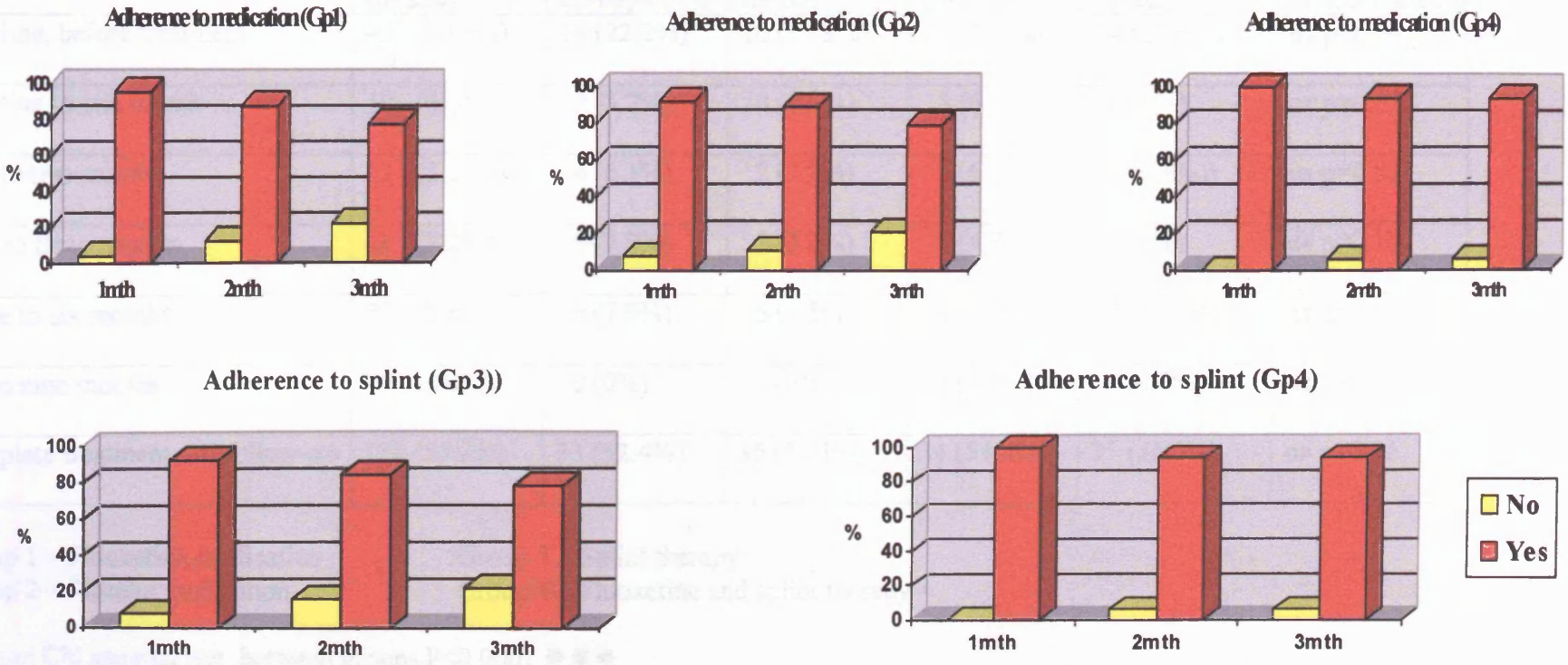


Table 64 : Time scale of withdrawal from treatment phase or follow up

Time scale:	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance between groups
Baseline, before treatment	49 (19.6%)	14 (22.2%)	10 (15.9%)	11(17.7%)	14 (22.6%)	**ns** p=0.73
Baseline to one month	10 (4.0%)	2 (3.2%)	4 (6.3%)	4 (6.5%)	0 (0%)	**ns** p=0.21
One to two months	13 (5.2%)	4 (6.3%)	2 (3.2%)	4 (6.5%)	3 (4.8%))	**ns** p=0.82
Two to three months	13 (5.2%)	5 (7.9%)	5 (3.2%)	3 (4.8%)	0 (0%)	**ns** p=0.15
Three to six months	22 (8.8%)	5 (7.9%)	6 (9.5%)	4 (6.5%)	7 (11.3%)	**ns** p=0.80
Six to nine months	5 (2.0%)	0 (0%)	0 (0%)	2 (3.2%)	3 (4.8%)	**ns** p=0.13
Complete treatment and follow-up	138 (55.2%)	33 (52.4%)	36 (57.1%)	34 (54.8%)	35 (56.5%)	**ns** p=0.95

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Pearson Chi squared test between groups P<0.0001 ✸✸✸

Table 65: Reasons for non adherence or withdrawl from treatment and follow up

Reasons	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance between groups
Pain gone	22 (8.8%)	8 (12.7%)	6 (9.5%)	4 (6.5%)	4 (6.5%)	ns p= 0.56
Time / travel problems	14 (5.6%)	3 (4.8%)	4 (6.3%)	3 (4.8%)	4 (6.5%)	ns p= 0.96
Moved away	8 (3.2%)	3 (4.8%)	2 (3.2%)	1 (1.6%)	2 (3.2%)	ns p= 0.80
Splint and run!	11 (4.4%)	0 (0%)	0 (0%)	10 (16.1%)	1 (1.8%)	*** p< 0.001
Does not want splint	8 (3.2%)	0 (0%)	0 (0%)	6 (9.7%)	2 (3.2%)	* p= 0.006
Does not want medication	7 (2.8%)	3 (4.8%)	2 (3.2%)	0 (0%)	2 (3.2%)	ns p= 0.43
Medical complications	5 (2.0%)	1 (1.6%)	1 (1.6%)	0 (0%)	3 (4.8%)	ns p= 0.27
Side effects	5 (2.0%)	2 (3.2%)	2 (3.2%)	0 (0%)	1 (1.6%)	ns p= 0.53
Other treatment	4 (1.6%)	0 (0%)	1 (1.6%)	1 (1.6%)	2 (3.2%)	ns p= 0.56
Work problems	4 (1.6%)	2 (3.2%)	2 (3.2%)	0 (0%)	0 (0%)	ns p= 0.26
Mental health problems	3 (1.2%)	1 (1.6%)	1 (1.6%)	0 (0%)	1 (1.6%)	ns p= 0.80
Pregnant	2 (0.8%)	1 (1.6%)	1 (1.6%)	0 (0%)	0 (0%)	ns p= 0.58
Family problems	1 (0.4%)	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)	ns p= 0.40
Reason unknown	17 (6.8%%)	6 (9.5%)	4 (6.3%)	2 (3.2%)	5 (8.1%)	ns p= 0.54

Table 66 :Adherence to medication

Time in weeks	Group1	Group 2	Group 4	Significance between groups
0	No 0 Yes 49	No 0 Yes 53	No 0 Yes 48	-
4	No 2 Yes 47	No 4 Yes 49	No 0 Yes 48	ns p=0.154
8	No 6 Yes 43	No 6 Yes 47	No 3 Yes 45	ns p=0.569
12	No 11 Yes 38	No 11 Yes 42	No 3 Yes 45	ns p=0.062

Table 67 : Adherence to occlusal appliance therapy

Time in weeks	Group 3	Group 4	Significance between groups
0	No 0 Yes 51	No 0 Yes 48	-
4	No 4 Yes 47	No 0 Yes 48	* p=0.048
8	No 8 Yes 43	No 3 Yes 45	ns p=0.135
12	No 11 Yes 40	No 3 Yes 45	* p=0.029

Table 68 : Adverse events recorded during physical therapy (splint wear)

Adverse event	Group 3 (n=51) Splint			Group 4 (n=48) Splint and fluoxetine		
Weeks	**4**	**8**	**12**	**4**	**8**	**12**
Splint lost	0 (0%)	0 (0%)	2 (3.9%)	0 (0%)	0 (0%)	0 (0%)
Splint broken	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	1 (2.1%)
Splint at home	1 (2.0%)	1 (2.0%)	2 (3.9%)	3 (6.3%)	1 (2.1%)	4 (8.3%)
Splint uncomfortable	4 (7.8%)	0 (0%)	4 (7.8%)	4 (8.3%)	0 (0%)	2 (4.2%)
Poor oral hygiene (Gross plaque deposits)	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6.3%)
Gingival inflammation	1 (2.0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)
Gingival swelling	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gingival bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gingival ulceration	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)

Table 69 : Adverse events reported during medical treatment phase

Weeks	Group 1 (SSRI)	Group 2 (Placebo)	Group 4 (SSRI + splint)	Group1 versus Group 2 OR (CI)	Group 4 versus Group 2 OR (CI)
4	15/47 (31.9%)	7/49 (14.3%)	15/48 (31.3%)	*2.8 (1.0-7.7)	*2.7 (1.0-7.5)
8	13/43 (30.2%)	8/47 (17.0%)	10/45 (22.2%)	2.1 (0.8-5.8)	2.0 (0.7-5.5)
12	12/38 (31.6%)	8/42 (19.0%)	12/45 (26.7%)	2.0 (0.7-5.5)	1.5 (0.6-4.3)

Table 70 : Adverse experience recorded during medical therapy

Adverse event	Group 1 SSRI (n=49)	Group 2 Placebo (n=53)	Group 4 SSRI+splint (n=48)	Group1 versus Group2	Group4 versus Group2
Digestive system				OR (CI)	OR (CI)
General gastric complaints	6 (12.2%)	3 (5.7%)	1 (2.1%)	2.3(0.5,9.9)	0.4(0.04,4)
Nausea	5 (10.2%)	1 (1.9%)	8 (16.7%)	5.9(0.7,52)	*10.4(1.2,86)
Diarrhoea	3 (6.1%)	1 (1.9%)	3 (6.3%)	3.4(0.3-33)	3.5(0.4,35)
Vomitting	0 (0%)	1 (1.9%)	2 (4.2%)	-	-
Anorexia	1 (2.0%)	0 (0%)	0 (0%)	-	-
Dry mouth	1 (2.0%)	2 (3.8%)	3 (6.3%)	0.5(0.1,5.9)	1.7(0.3,11)
Nervous system					
Headache	3 (6.1%)	3 (5.7%)	4 (8.3%)	1.1(0.2,5.7)	1.5(0.3,7.1)
Insomnia	5 (10.2%)	1 (1.9%)	4 (8.3%)	5.9(0.7,52)	4.7(0.5,44)
Drowsiness	6 (12.2%)	1 (1.9%)	3 (6.3%)	7.3(0.8,62)	3.5(0.35,35)
Dizzieness	0 (0%)	1 (1.9%)	3 (6.3%)	-	-
Skin					
Rash	3 (6.1%)	3 (5.7%)	6 (12.5%)	1.1(0.2,5.7)	2.4(0.6,10)
Sweating	1 (2.0%)	0 (0%)	2 (4.2%)	-	-
Urogenital system					
Sexual dysfunction	0 (0%)	0 (0%)	1 (2.1%)	-	-
Other adverse event					
URTI (cold, cough) flu-like symptoms, malaise musculoskeletal pain, fatigue,.	7(14.3%)	3 (5.7%)	4 (8.3%)	2.8(0.7,11)	1.5(0.32,7.2)

9. 2 FOLLOW – UP PHASE

9.2.0 Follow up phase

9.2.1 Maintenance and amelioration in overall pain severity and intensity (Fig. 63)

Illustrated graphically, it is clear a significant reduction in pain severity (MPI severity) (figure 63a) occurs at the end of the three month trial programme which, after discontinuation of treatment, is then sustained during the follow-up phase within all four treatment groups. Similar findings were found in MPQ present pain intensity , MPQ,total %(fig. 63b), VAS (clinical report) (fig. 63c), VAS (self-report) (fig. 63d)

9.2.2 Verbal rating scales **9.2.2.1 Visual analogue scale VAS (clinical report)**

9.2.2.1.1 VAS (Imputation analysis) (Table 71, Figure 64)

Analysing all groups together, using the repeated measures ANOVA, there was a clearly significant improvement in VAS even during the follow-up phase F(2) 8.93, $p<0.001$. Multivariate tests Wilk's lambda $F(2,248) =7.60, p=0.001$, suggested a significant improvement in the mean recorded VAS during the follow-up phase of a significantly linear trend $F(1)=14.30, p<0.001$. Paired sample t-tests of all groups together showed the mean VAS had been maintained three months post therapy, having minimally decreased from 4.06 (2.57) to 3.91 (2.66) a non significant improvement. However, six months post therapy the mean VAS scale was recorded as 3.56 (2.68), a small but nonetheless significant improvement of 0.5mm, $p<0.001$. Amongst each group, all scores were maintained and even appeared to improve post therapy but only groups 2 and 3 showed a significant improvement of 0.5mm, $F(2)3.74, p=0.026$ and 0.7mm $F(2)$ 8.84, $p=0.001$ respectively. Such small changes in score would not be considered clinically relevant.

Inter group analysis, using the parametric one-way ANOVA, revealed no significant difference in VAS improvement during the follow-up phase.

9.2.2.1.2 VAS (Completers analysis) (Table 72, figure 65)

Analysing all groups together , the repeated measures ANOVA for within-subjects effect, revaled a significant maintenance and improvement in VAS $F(2) = 8.1, p<0.001$, as were the multivariate tests Wilk's lambda $F(2,248)=5.04, p=0.001$ suggesting significant difference in measurement during the follow-up phase of a significantly linear trend $F(1)$ 13.98,$p<0.001$. Paired sample t-tests for all groups were only significant between the end of treatment and end of follow-up with an improvement of 0.3mm, from 3.25(2.41) to 3.58(2.68) at treatment end, $p<0.001$.

Within groups only group 3 showed a significant improvement of 1.2mm from 3.19 (2.22) at treatment end to 1.99 (1.78) at end of follow-up, $F(2)$ 9.76,$p=0.001$. This was a significantly linear trend $F(1)$ 15.08,$p=0.001$. Again such minimal changes of mm's in VAS scores do not serve any clinical relevance and inter group analysis showed no significant difference in improvement between groups.

9.2.2.1.3 Relapse in VAS (Table 73)

Relapse in scores were not significant either within or between groups, using McNemar tests for intra group analysis and χ^2 for intergroup analysis.

9.2.2.2 PPI (Non/mild/moderate/severe) (Table 74, Figure 66)

PPI was maintained and significantly improved during follow up amongst all the study participants, $\chi^2=(2)16.17$, $p<0.001$. Those with none or mild pain increased from 154/250 (61.6%) at the end of treatment to 168/250 (67.2%) at the end of follow up. This remained significant in intra group analysis in group 2 $\chi^2=(2)$ 8.72, $p=0.013$ and group 3 $\chi^2=(2)$ 6.60, $p=0.037$ but inter group analysis showed no significant difference between groups.

9.2.2.3 Pain response (Worse / In pain / Improved / Pain free) (Table75,Figure 67)

Results indicate slight improvement in scores with no significant relapse during the follow up phase amongst the combined study participants χ^2=(2)7.92, p=0.019. There was no significant difference between the four groups.

9.2.2.4 Frequency (Never / Occasionally / Often / Always) (Table 76, Figure 68)

Frequency of pain actually improved during follow up with 87/250 (35%) with never or occasional pain at the end of treatment increasing to 117/250 (47%) by the end of follow up χ^2=(2)14.48,p=0.001. This remained significant in group 4 analysis χ^2=(2)7.10, p=0.029 but there was no proven significance between groups.

9.2.2.5 Interference (Yes / no) (Table 77, Figure 69)

There was significant reduction in pain interference of 120/250 (48%) at three months which was maintained and further reduced during follow up 104/250 (42%) Cochrane Q=(2) 7.42, p=0.024 . Interference appeared to decrease most significantly in group 3 from 29/62 (46.8%) to 22/62 (35.5%), Cochrane Q=(2)7.17, p=0.028. However, this was not found to be significant between groups.

Figure 63a: Pain severity – MPI severity (median scores)

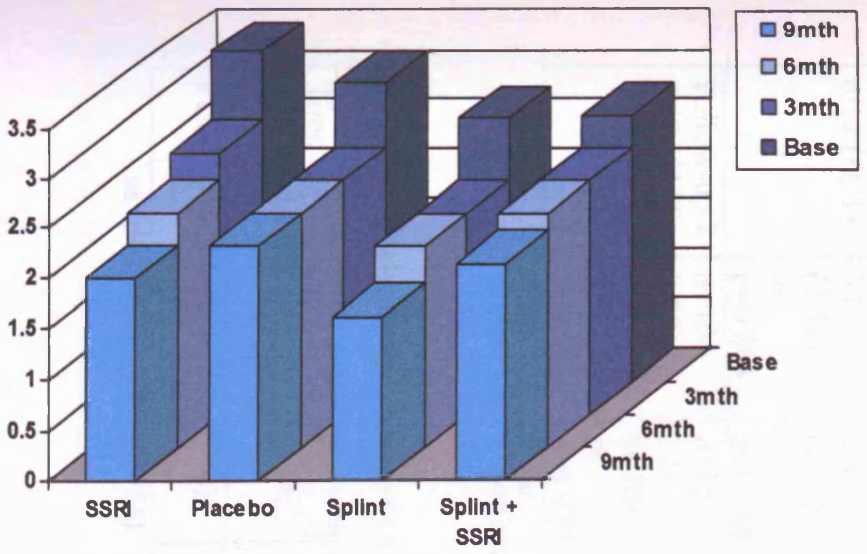


Figure 63b: MPQ – total% (median scores)

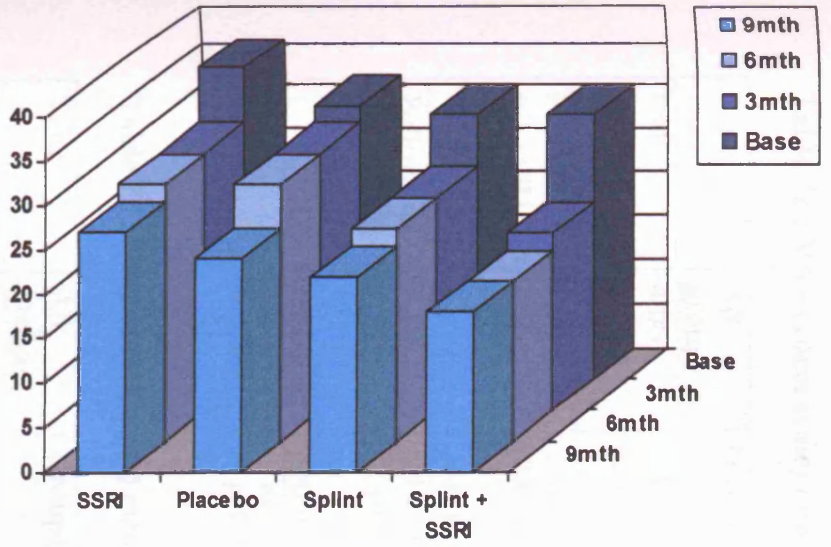


Figure 63c: VAS (clinical report) median scores

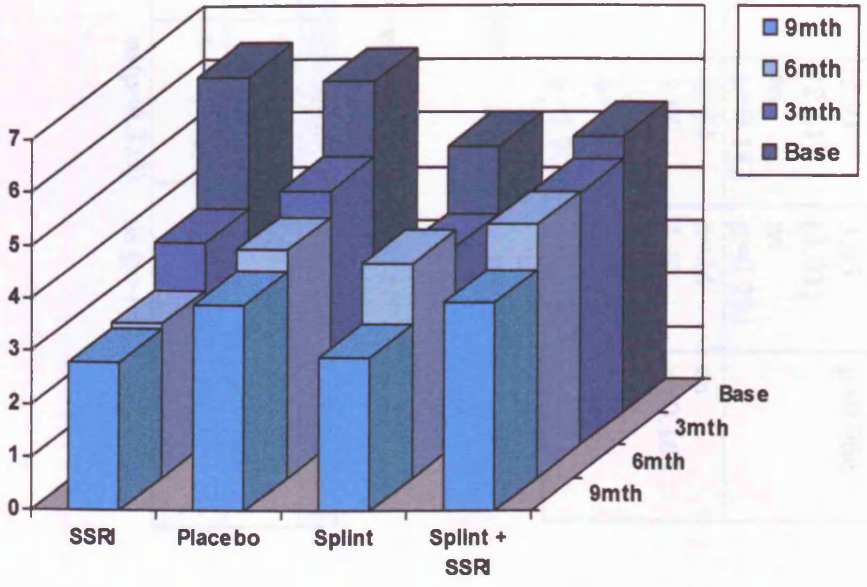


Figure 63d: VAS (self report) median scores

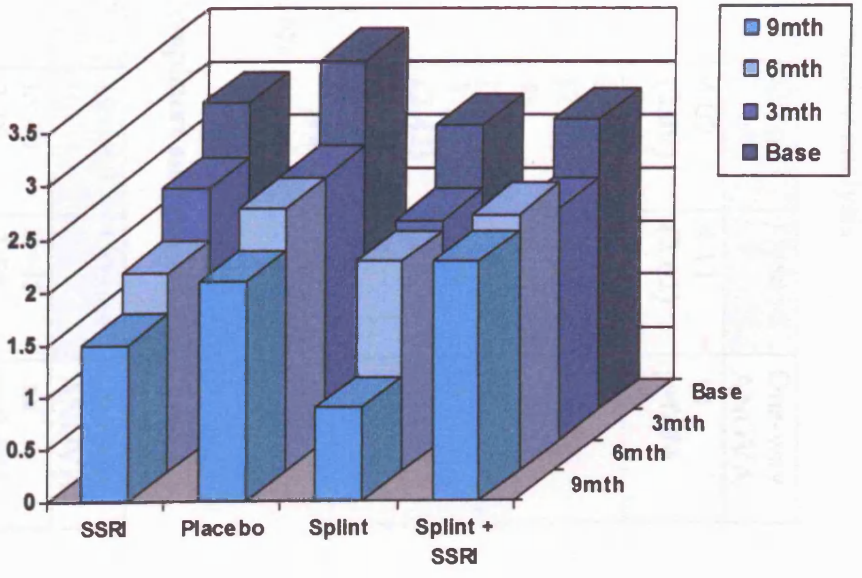


Table 71 : VAS (10cm scale) mean (+/- SD) Imputation analysis

Time	All groups	Group1	Group2	Group3	Group4	One-way ANOVA
End treatment 3/12	4.06 (2.57)	3.80 (2.81)	4.31 (2.46)	4.02 (2.39)	4.11 (2.62)	ns p=0.74
Follow-up 1 6/12 (FU1)	3.91 (2.66) ns p=0.164	3.50 (2.97) ns p=0.167	4.06 (2.44) ns p=0.20	3.76 (2.37) ns p=0.117	4.31 (2.82) ns p=0.487	ns p=0.35
Follow-up 2 9/12 (FU2)	3.58 (2.68) *** p<0.001	3.33 (3.30) ns p=0.072	3.78 (2.69) * p=0.013	3.37 (2.42) ** p=0.001	3.85 (2.57) ns p=0.449	ns p=0.59
	*** p<0.001	ns p=0.129	* p=0.026	** p=0.001	ns p=0.342	

Table 72 : VAS (10cm scale) mean (+/- SD) Completers analysis

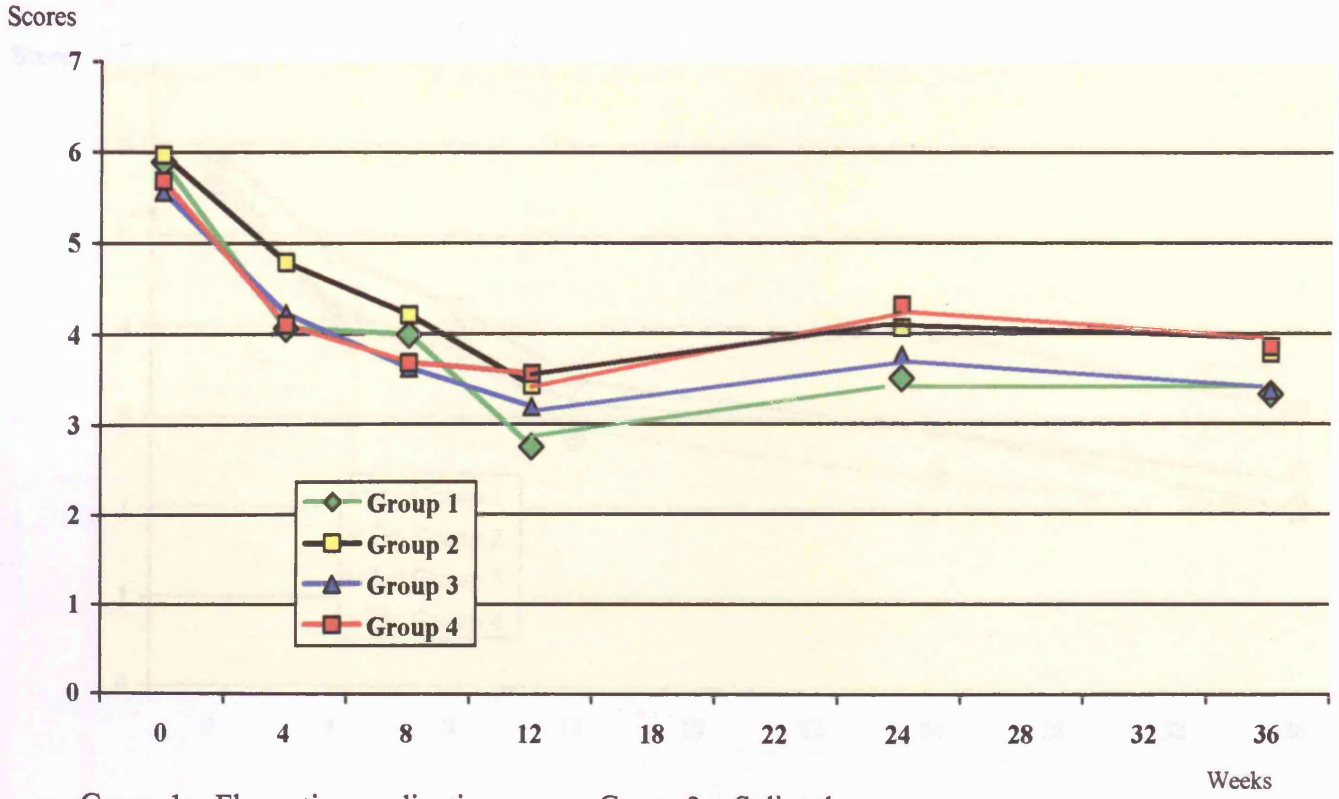
Time	All groups	Group1	Group2	Group3	Group4	One-way ANOVA
End treatment 3/12	n=165 3.25 (2.41)	n=38 2.75 (2.48)	n=42 3.43 (2.32)	n=40 3.19 (2.22)	n=45 3.56 (2.61)	ns p=0.453
Follow-up 1 6/12 (FU1)	n=138 3.03 (2.52) ns p=0.265	n=35 2.37 (2.61) ns p=0.168	n=34 2.90 (2.07) ns p=0.203	n=35 2.93 (2.11) ns p=0.183	n=34 3.95 (3.01) ns p=0.291	ns p=0.066
Follow-up 2 9/12 (FU2)	n=135 3.58 (2.68) *** p<0.001	n=35 2.06 (2.58) ns p=0.072	n=35 2.41 (2.29) ns p=0.012	n=31 1.99 (1.78) ** p=0.001	n=34 3.12 (2.35) ns p=0.406	ns p=0.165
	*** p<0.001	ns p=0.129	ns p=0.062	** p=0.001	ns p=0.427	

Table 73 : Relapse in VAS score during follow-up numbers (%) N=250

Time	All groups	Group 1	Group2	Group3	Group4	Significance
FU1	46 (18.4%)	10 (15.9%)	10 (15.9%)	9 (14.5%)	17 (27.4%)	ns p=0.211
FU2	43 (17.2%)	12 (19%)	9 (14.3%)	6 (9.7%)	16 (25.8%)	ns p=0.102
	ns (p=0.735)	ns (p=0.754)	ns (p=1.0)	ns(p=0.375)	ns (p=1.0)	

Figure 64: VAS (visual analogue scale)
A comparison of mean scores showing maintenance and continued improvement in scores during follow-up.

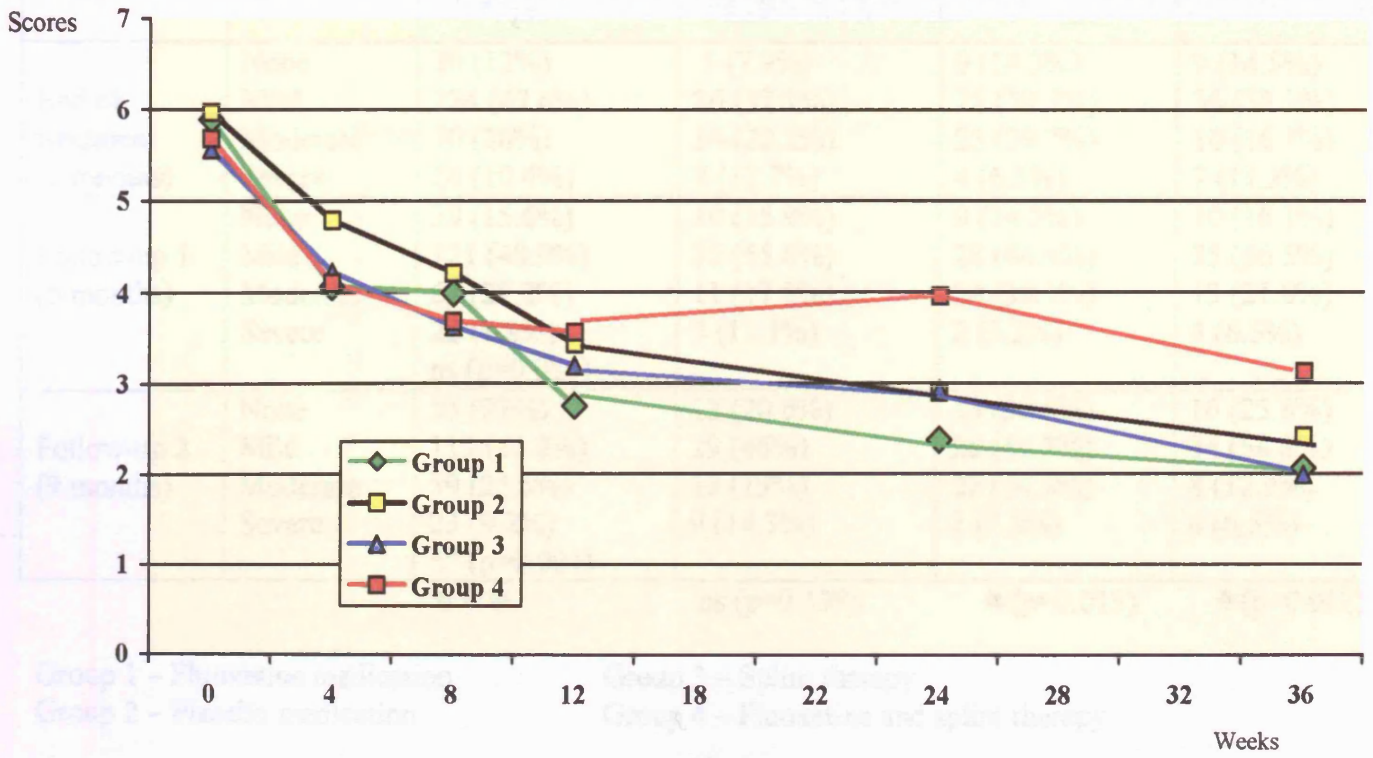
Imputation analysis showing three month (week 12) treatment and follow-up at six months (week 24) and nine months (week36).



Group 1 – Fluoxetine medication
Group 2 – placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Figure 65: VAS (visual analogue scale)
A comparison of mean scores showing maintenance and continued improvement in scores during follow-up.

Completers analysis showing three month (week 12) treatment and follow-up at six months (week 24) and nine months (week36).



Group 1 – Fluoxetine medication
Group 2 – placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

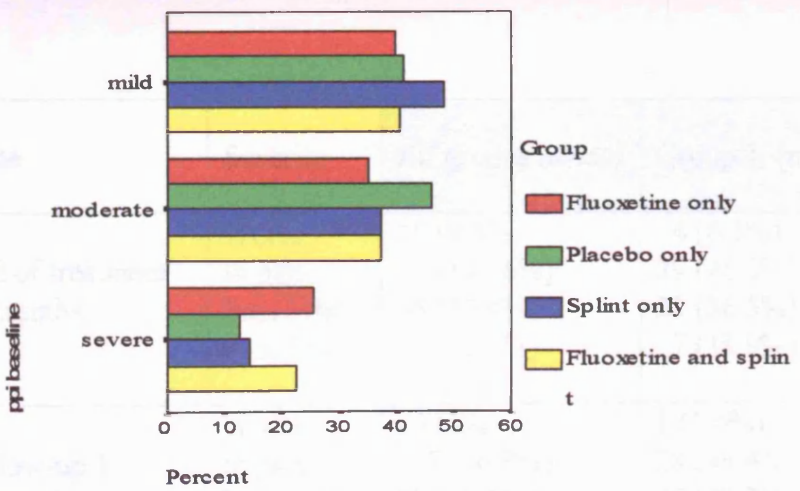
Table 74: Present pain intensity scores (PPI) (Intention to treat, imputation analysis) during follow-up.

Time	PPI	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance
End of treatment (3 months)	None Mild Moderate Severe	30 (12%) 124 (49.6%) 70 (28%) 26 (10.4%)	5 (7.9%) 36 (57.1%) 14 (22.2%) 8 (12.7%)	9 (14.3%) 25 (39.7%) 25 (39.7%) 4 (6.3%)	9 (14.5%) 36 (58.1%) 10 (16.1%) 7 (11.3%)	7 (11.3%) 27 (43.5%) 21 (33.9%) 7 (11.3%)	ns p=0.384
Follow-up 1 (6 months)	None Mild Moderate Severe	39 (15.6%) 121 (48.9%) 68 (27.2%) 22 (8.8%) ns (p=0.083)	10 (15.9%) 35 (55.6%) 11 (17.5%) 7 (11.1%)	9 (14.3%) 28 (44.4%) 24 (38.1%) 2 (3.2%)	10 (16.1%) 35 (56.5%) 13 (21.0%) 4 (6.5%)	10 (16.1%) 23 (37.1%) 20 (32.3%) 9 (14.5%)	ns p=0.255
Follow-up 2 (9 months)	None Mild Moderate Severe	55 (22%) 113 (45.2%) 59 (23.6%) 23 (9.2%) ** (p=0.001)	13 (20.6%) 29 (46%) 12 (19%) 9 (14.3%)	13 (20.6%) 26 (41.3%) 22 (34.9%) 2 (3.2%)	16 (25.8%) 34 (54.8%) 8 (12.9%) 4 (6.5%)	13 (21%) 24 (38.7%) 17 (27.4%) 8 (12.9%)	ns p=0.189
		✸✸✸	ns (p=0.199)	✸(p=0.013)	✸(p=0.037)	ns (p=0.325)	

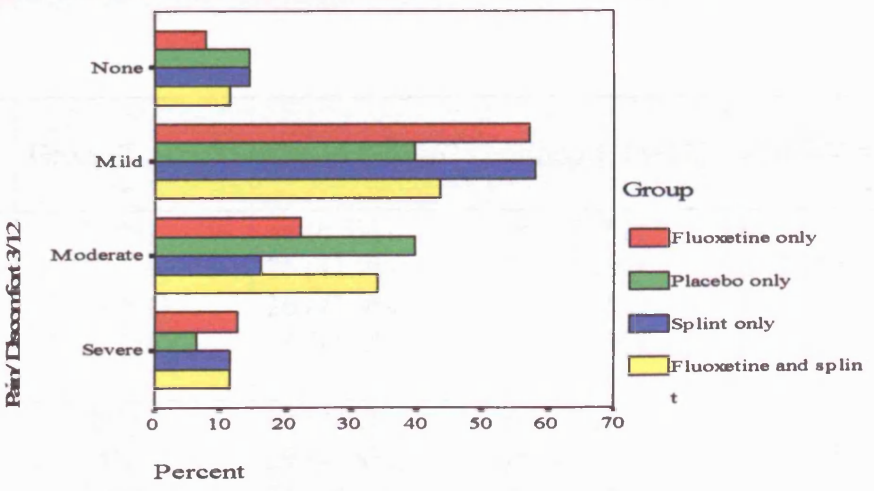
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001✸✸✸ Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant)

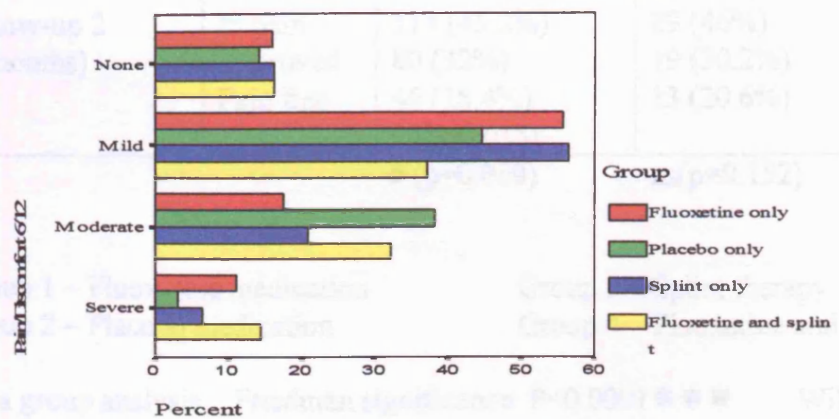
Figure 66 : Pain intensity at baseline



Pain intensity at 12 weeks (Treatment end)



Pain intensity at 24 weeks (3 months post therapy)



Pain intensity at 36 weeks (6 months post therapy)

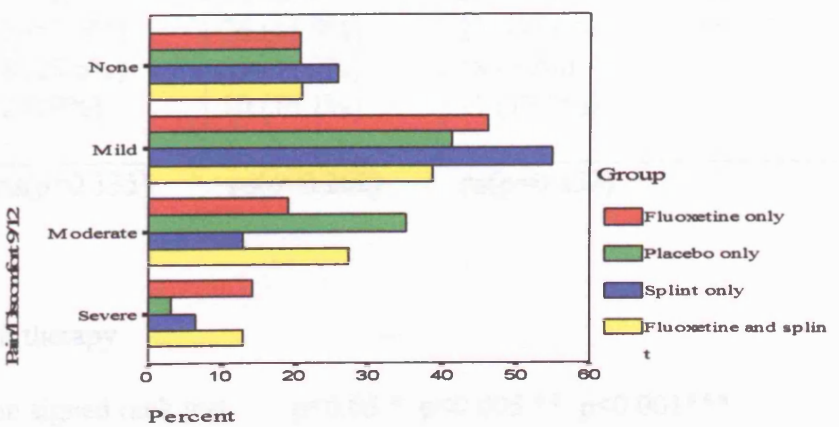


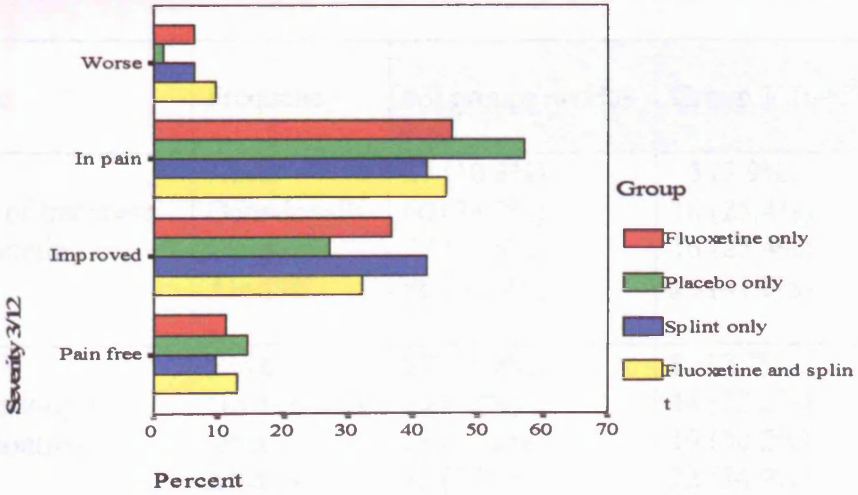
Table 75: Pain severity: Worse / In pain / Improved / Pain free– (Intention needed to treat, imputation analysis) during follow-up

Time	Severity	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance
End of treatment (3 months)	Worse In pain Improved Pain free	15 (9.3%) 119 (47.6%) 86 (34.4%) 30 (12.0%)	4 (6.3%) 29 (46.0%) 23 (36.5%) 7 (18.9%)	1 (1.6%) 36 (57.1%) 17 (39.5%) 9 (20.9%)	4 (6.5%) 26 (41.9%) 26 (41.9%) 6 (15.8%)	6 (13.9%) 28 (45.2%) 18 (32.3%) 8 (12.9%)	ns p=0.950
Follow-up 1 (6 months)	Worse In pain Improved Pain free	10 (4%) 117 (46.8%) 89 (35.6%) 34 (13.6%) ns (p=0.154)	1 (1.6%) 28 (44.4%) 25 (39.7%) 9 (14.3%)	2 (3.2%) 34 (54%) 18 (28.6%) 9 (14.3%)	1 (1.6%) 29 (46.8%) 24 (38.7%) 8 (12.9%)	6 (9.7%) 26 (41.9%) 22 (35.5%) 8 (12.9%)	ns p=0.655
Follow-up 2 (9 months)	Worse In pain Improved Pain free	11 (4.4%) 113 (45.2%) 80 (32%) 46 (18.4%) * (p=0.015)	2 (3.2%) 29 (46%) 19 (30.2%) 13 (20.6%)	0 (0%) 33 (52.4%) 18 (28.6%) 12 (19%)	1 (1.6%) 26 (41.9%) 25 (40.3%) 10 (16.1%)	8 (12.9%) 25 (40.3%) 18 (29%) 11 (17.7%)	ns p=0.624
		✸(p=0.019)	ns(p=0.152)	ns(p=0.135)	ns(p=0.262)	ns(p=0.839)	

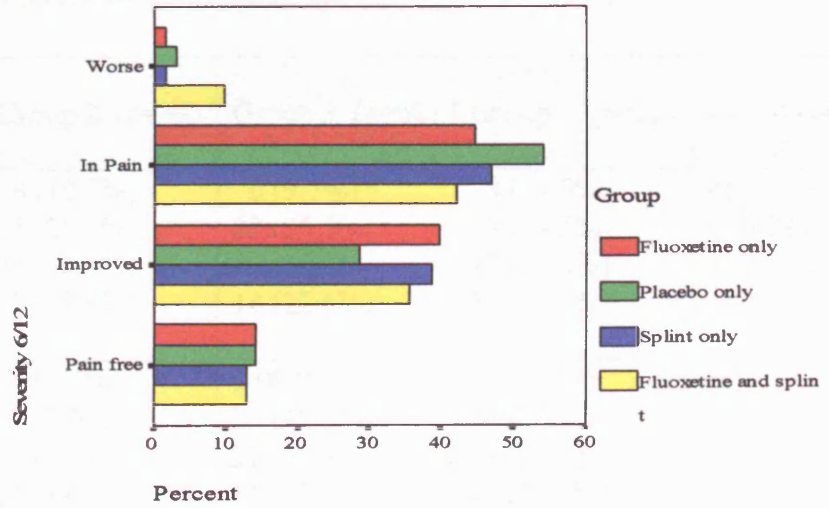
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001✸✸✸ Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant)

Figure 67: **Pain response at 12 weeks (Treatment end)**



Pain response at 24 weeks (3 months post therapy)



Pain response at 36 weeks (6 months post therapy)

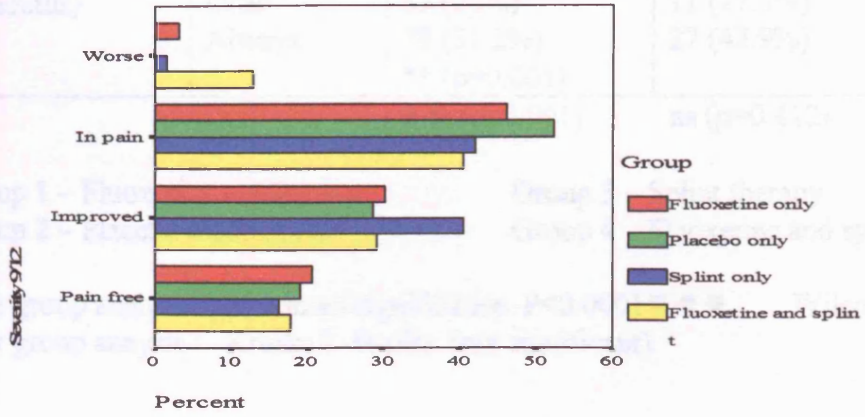


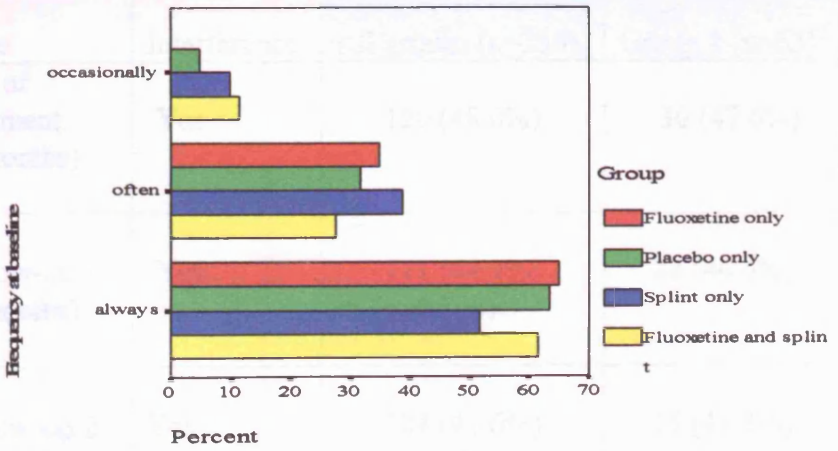
Table 76: Frequency scores (Intention needed to treat, imputation analysis) during follow-up

Time	Frequency	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance
End of treatment (3 months)	Never Occasionally Often Always	27 (10.8%) 60 (24.0%) 77 (30.8%) 86 (34.4%)	5 (7.9%) 16 (25.4%) 16 (25.4%) 26 (41.3%)	8 (12.7%) 13 (20.6%) 24 (38.1%) 18 (28.6%)	6 (9.7%) 22 (35.5%) 20 (32.3%) 14 (22.6%)	8 (12.9%) 9 (14.5%) 17 (27.4%) 28 (45.2%)	ns p=0.083
Follow-up 1 (6 months)	Never Occasionally Often Always	27 (10.8%) 70 (28%) 68 (27.2%) 85 (34%) ns (p=0.297)	8 (12.7%) 14 (22.2%) 19 (30.2%) 22 (34.9%)	7 (11.1%) 17 (27%) 15 (23.8%) 24 (38.1%)	5 (8.1%) 25 (40.3%) 21 (33.9%) 11 (17.7%)	7 (11.3%) 14 (22.6%) 13 (21%) 28 (45.2%) ns (p=0.590)	ns p=0.108
Follow-up 2 (9 months)	Never Occasionally Often Always	36 (14.4%) 81 (32.4%) 55 (22%) 78 (31.2%) ** (p=0.001)	9 (14.3%) 16 (25.4%) 11 (17.5%) 27 (42.9%)	9 (14.3%) 23 (36.5%) 13 (20.6%) 18 (28.6%)	8 (12.9%) 25 (40.3%) 19 (30.6%) 10 (16.1%)	10 (16.1%) 17 (27.4%) 12 (19.4%) 23 (37.1%) * (p=0.014)	ns p=0.169
		✸✸ (p=0.001)	ns (p=0.412)	ns (p=0.065)	ns (p=0.185)	✸(p=0.029)	

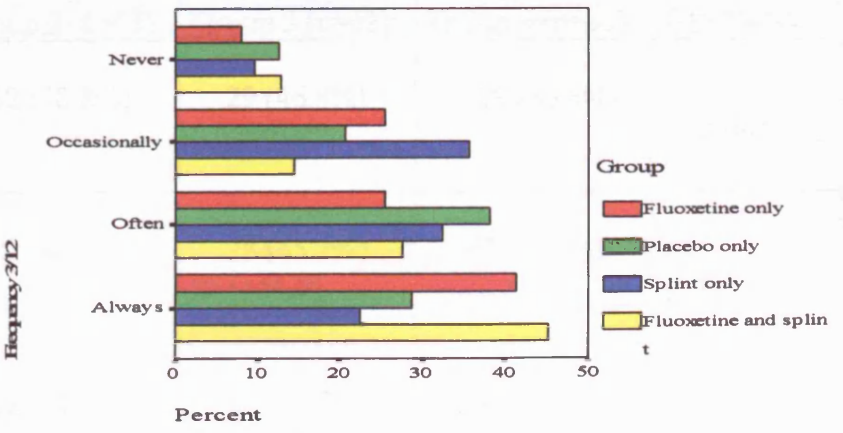
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Intra group analysis : Friedman significance P<0.0001✸✸✸ Wilcoxon signed rank test p<0.05 * p<0.005 ** p<0.001***
Inter group anaysis : Kruskall -Wallis (not significant)

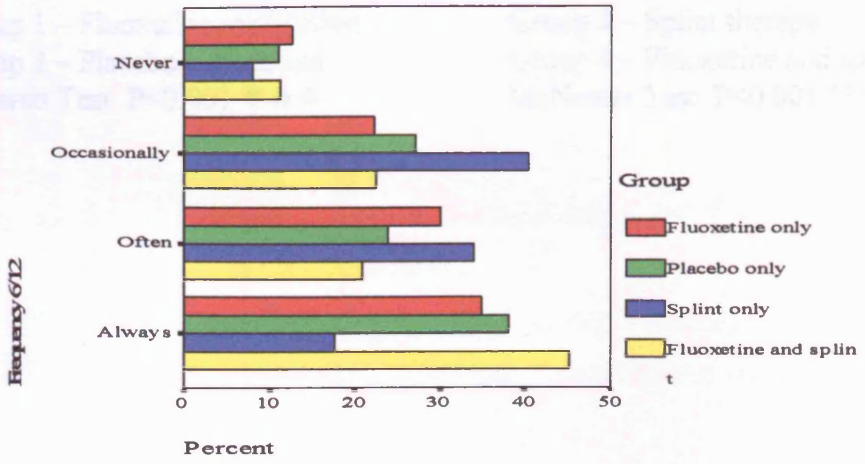
Figure 68: **Frequency at baseline**



Frequency at 12 weeks (Treatment end)



Frequency at 24 weeks (3 months post therapy)



Frequency at 36 weeks (6 months post therapy)

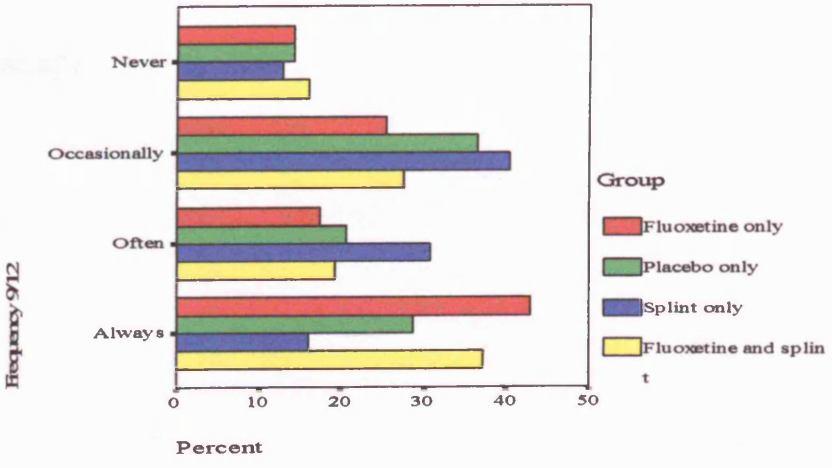


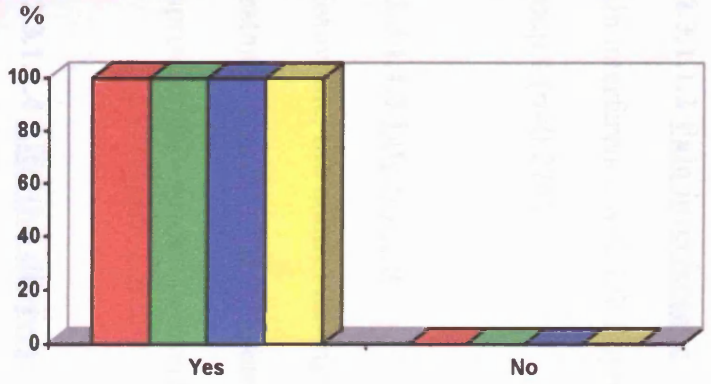
Table 77: **Secondary outcome measure** – Interference with life (Intention to treat, imputation analysis) during follow-up.

Time	Interference	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Significance
End of treatment (3 months)	Yes	120 (48.0%)	30 (47.6%)	32 (50.8%)	29 (46.8%)	29 (46.8%)	ns p=0.965
Follow-up 1 (6 months)	Yes	111 (44.4%) ns (p=0.188)	28 (44.4%)	28 (44.4%)	28 (45.2%) ns (p=1.0)	27 (43.5%)	ns p=0.998
Follow-up 2 (9 months)	Yes	104 (41.6%) * (p=0.012)	26 (41.3%)	28 (44.4%)	22 (35.5%) * (p=0.016)	28 (45.2%)	ns p=0.684
		✸ (p=0.024)	ns (p=0.424)	ns (p=0.202)	✸(p=0.028)	ns (p=0.829)	

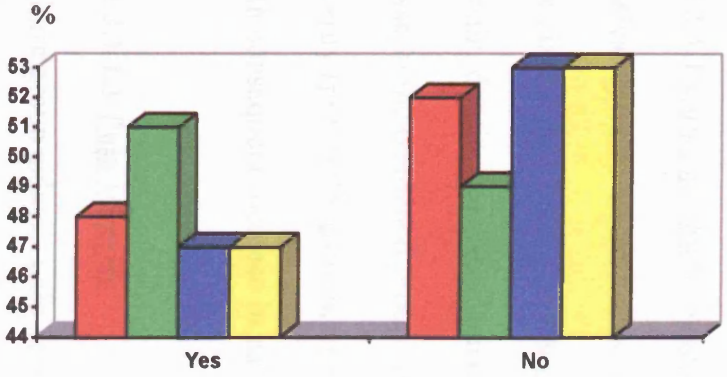
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Cochran Test P<0.001 ✸✸✸
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
McNemar Test P<0.001 ***

Figure: 69

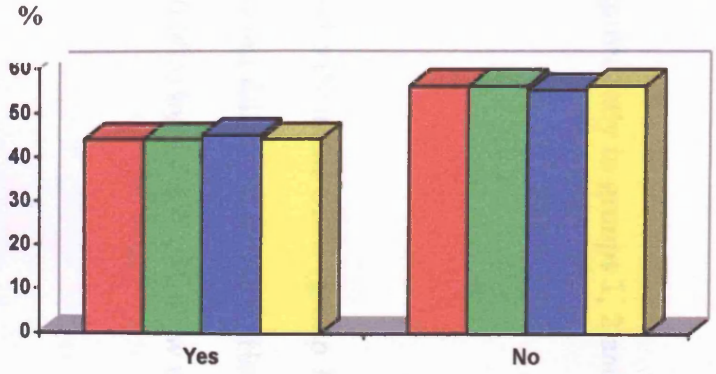
Interference with life at baseline



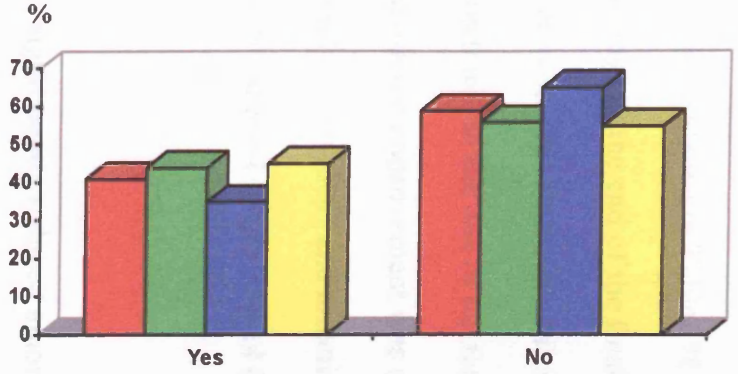
Interference with life at 12 weeks (Treatment end)



Interference with life at 24 weeks (3 months post therapy)



Interference with life at 36 weeks (6 months post therapy)



Group 1 (Fluoxetine)
Group 2 (Placebo)
Group 3 (Splint)
Group 4 (Fluoxetine and splint)

9.2.3 Self-Report pain questionnaires

9.2.3.1 MPI - Follow up summary (Illustrated in figure 70)

9.2.3.1.1 Comparison to baseline recordings (shown in Tables 78)

Analysing treatment from baseline recordings to the end of the final follow up phase there is clearly a significant improvement in several elements of the patient's perspective of pain, despite the discontinuation of treatment at the end of the three month treatment phase.In the combined group cohort, significant improvement was observed in pain severity ($p<0.001$), pain interference with life ($p<0.001$) and affective distress ($p<0.001$) with consequent increase in patients perceived level of life control ($p<0.001$)

9.2.3.1.1.1 Pain severity

In intra group anlayis, pain severity was significantly reduced amongst all individual groups, 1,2,3,and 4 ($p<0.001$).

9.2.3.1.1.2 Pain interference

Pain interference with life improved significantly in groups 1, 2 and 3, ($p<0.001$) but not group 4 ($p=0.276$).

9.2.3.1.1.3 Life control

Meanwhile, life control having improved only in the SSRI (group 1) at the end of the treatment phase was also maintained during follow up $p=0.007$. However, an additional improvement was seen in group 3, ($p=0.006$) by the end of follow up.

9.2.3.1.1.4 Affective distress

Affective distress had significantly improved in medical therapy groups 1,2 and 4 at the

end of treatment and this was clearly maintained in group 1 during follow up $p<0.001$. However, there was no between group significance.

9.2.3.1.1.5 Response of significant other – support

The anomaly of reduced support by significant family and friends, seen in group 3 at the end of treatment, was also reiterated during follow up with significance in group 3, $p=0.002$.

9.2.3.1.1.6 Inter group analysis

Despite all the above observations, intergroup analysis revealed no significant difference between groups amongst any of the variables.

9.2.3.1.2 Comparison to end of treatment recordings (Table 79)

Analysing improvement since treatment completion, we see there is only a significant improvement in severity and interference, $p<0.001$. This was mirrored by the results for group 3 $p<0.001$ but only interference reached significant improvement in group 1 $p=0.047$ and group 2 $p=0.033$. The median change in all MPI scores during follow up is zero, indicating a generalised maintenance of treatment effect.

9.2.3.2 MPQ, BDI, Kellner – Follow-up summary (shown in Figure 71)

9.2.3.2.1 Comparison to baseline recordings (shown in Table 80)

Analysing treatment from baseline to end of final follow up, there is a significant difference amongst combined groups in VAS, PPI, total %, sensory %, affective %, BDI, Kellner illness attitude and hypochondriacal beliefs, $p<0.001$. PPI improved similarly in groups 1,2 and 3 $p<0.001$ and to a lesser extent in group 4 $p=0.005$.

MPQ VAS improved most significantly in group 3 $p<0.001$ and to a lesser extent in group 2 $p=0.005$ and group 4 $p=0.006$. MPQ total% improved significantly amongst all individual groups $p<0.001$.MPQ sensory% improved significantly in groups 3 and 4 $p<0.001$ and to a slightly lesser extent in group 1, $p=0.002$ and group 2, $p=0.001$.MPQ affective % improved significantly in group 1 $p=0.002$, group 2 $p<0.001$ and group 3 $p=0.002$. BDI however, improved most significantly in group 1, $p<0.001$, group2, $p=0.001$ and group 3, $p=0.032$ and group 4, $p=0.028$. Kellner illness attitude and hypochondriacal beliefs were only improved in group 1 $p=0.002$ and $p=0.006$ respectively.

The median change in score during follow up is zero, again indicating an overall maintenance of improvement since treatment end. Within groups this varies but is not significant between groups.

9.2.3.2.2 <u>Comparison to end of treatment recordings</u> (Table 81)

Improvement since treatment completion and final follow up is significant amongst combined groups in VAS, MPQ: total %, sensory %, affective, BDI, Kellner illness attitude and hypochondriacal beliefs, $p<0.001$.Differences occurred within groups with PPI most significantly improved in group1,2 and 3, $p<0.001$ and to a lesser extent in group 4,$p=0.005$. MPQ VAS was significantly reduced in group 3 $p<0.001$ and to a lesser extent in group 2, $p=0.005$ and group 4, $p=0.006$. MPQ total % was significantly improved in each individual group $p<0.001$.MPQ sensory % was reduced in groups 3 and 4, $p<0.001$, group 1, $p=0.002$ and group 2, $p=0.001$. MPQ affective % was reduced in groups 1 and 3, $p=0.002$ and group 2, $p<0.001$.BDI composite scores were most significantly reduced during follow-up in group 1, $p<0.001$, group 2, $p=0.001$ and to a lesser extent in group 3, $p=0.032$ and group 4 $p=0.028$. Kellner illness attitude and

hypochondriacal beliefs was only significantly reduced in group 1, p=0.002 and p=0.006 respectively.

9.2.3.3 Relapse in MPI, MPQ, BDI and Kellner scores since end of treatment

(Table 821 and figures 72 and 73).

Maintenance and improvement in post treatment scores were 80-90% without significance between groups. For example maintenance and improvement in scores for MPI severity averaged zero at follow up 1 and 0.33 at follow up 2.In other words, an overall maintenance of score but no further improvement at the three month post treatment follow-up was recorded and an actual improvement in score at the six month post treatment follow up. The relapse in score which occurred was approximately 18% three months post treatment at FU1, and 16%, six months post treatment at FU2.

Table 78: Multidimensional Pain inventory (MPI) A comparison of median scores (25^{th},75^{th} percentiles) (Imputation analysis)

MPI	Study	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Sig.
Patients perspective of pain							
MPI - Severity	Start	3.00 (1.92,4.00)	3.33 (2.00,4.33)	3.00 (2.33,4.00)	2.66 (1.33,3.40)	2.66 (1.65,4.00)	ns p=0.105
	Finish	2.33 (1.30,3.66) ***	2.60 (1.30,4.00)**	2.33 (1.33,3.66) ***	2.00 (0.66,3.00) ***	2.33 (1.33,3.75) *	ns p=0.298
	FU1	2.33 (1.30,3.37) ***	2.33 (1.33,4.00)***	2.33 (1.33,3.33) ***	2.00 (0.66,3.00) ***	2.33 (1.00,4.00) *	ns p=0.406
	FU2	2.00 (1.00,3.66) ***	2.00 (1.00,4.00)***	2.33 (1.00,3.60) ***	1.63 (0.58,2.66) ***	2.15 (0.92,3.75) **	ns p=0.130
		***	***	***	***	***	
MPI - Interference	Start	1.45 (0.65,2.88)	1.90 (0.82,3.36)	1.63 (0.80,2.90)	1.36 (0.45,2.27)	1.24 (0.52,2.65)	ns p=0.103
	Finish	1.05 (0.36,2.38)***	1.30 (0.36,2.72)	1.16 (0.54,2.54) ***	0.90 (0.29,2.27) *	1.00 (0.43,2.40)	ns p=0.684
	FU1	1.00(0.36,2.32) ***	1.09 (0.55,2.73) *	0.82 (0.36,2.54) ***	0.85 (0.18,2.18) ***	1.00 (0.43,2.50)	ns p=0.350
	FU2	0.95(0.27,2.21) ***	0.90 (0.30,2.72) **	0.90 (0.36,2.00) ***	0.58 (0.90,2.19) ***	1.09 (0.27,2.40)	ns p=0.532
		***	***	***	***	ns (p=0.276)	
MPI – Life control	Start	3.25 (2.31,4.00)	3.25 (2.00,4.00)	3.25 (2.25,4.25)	3.25 (2.46,4.00)	3.38 (2.50,4.25)	ns p=0.780
	Finish	3.50 (2.50,4.25) ***	3.50 (2.75,4.50) **	3.50 (2.50,4.00)	3.50 (2.50,4.25)	3.50 (2.50,4.25)	ns p=0.952
	FU1	3.50 (2.50,4.25) ***	3.50 (2.50,4.50) *	3.75 (2.75,4.25)	3.25 (2.50,4.25) *	3.50 (2.50,4.56)	ns p=0.746
	FU2	3.50 (2.75,4.50) ***	3.50 (2.75,4.50) **	3.75 (3.00,4.25)	3.50 (2.75,4.25) **	3.50 (2.50,4.75) *	ns p=0.909
		***	* (p=0.007)	ns (p=0.173)	* (p=0.006)	ns (p=0.206)	
MPI – Affective distress	Start	3.33 (2.33,4.30)	3.60 (2.60,4.33)	3.60 (2.65,4.40)	3.00 (2.00,4.00)	3.32 (2.32,4.30)	ns p=0.063
	Finish	3.00 (2.00,4.00) ***	3.30 (2.00,4.00) **	3.33 (2.00,4.00) **	3.00 (1.92,4.00)	2.83 (2.00,3.62) *	ns p=0.590
	FU1	3.00 (2.00,3.66) ***	3.00 (1.66,4.00)***	3.00 (2.00,4.00) *	3.00 (1.65,4.00)	3.00 (1.66,3.60) *	ns p=0.551
	FU2	3.00 (1.92,4.00) ***	3.00 (1.66,4.00)***	3.33 (2.30,4.00)	3.00 (1.60,4.00)	2.66 (1.60,3.40) *	ns p=0.257
		***	***	* (p=0.012)	ns (p=0.059)	ns (p=0.054)	
Response significant other							
MPI – Support response	Start	3.33 (2.30,4.66)	3.60 (2.25,4.66)	3.66 (2.32,5.00)	3.00 (2.33,4.33)	3.00 (2.00,4.33)	ns p=0.681
	Finish	3.33 (2.32,4.33)	3.33 (2.33,4.33)	3.33 (2.33,5.00)	3.00 (1.70,4.00) **	3.60 (2.17,4.47)	ns p=0.300
	FU1	3.33 (2.00,4.33) *	3.33 (2.00,4.33)	3.33 (1.83,4.66)	3.00 (1.83,4.00) *	3.33 (2.33,4.00)	ns p=0.491
	FU2	3.00 (2.00,4.33) **	3.00 (2.00,4.33)	3.66 (2.32,4.66)	3.00 (1.60,4.00) *	3.15 (2.00,4.31)	ns p=0.103
		*(p=0.013)			**(p=0.002)		
MPI – Punishing response	Start	1.00 (0,2.06)	0.75 (0.25,2.81)	1.25 (0.25,2.56)	0.75 (0,2.00)	0.75 (0,1.75)	ns p=0.201
	Finish	1.00 (0,2.00)	1.00 (0,2.5)	1.25 (0.25,2.00)	1.00 (0,2.00)	1.00 (0,1.75)	ns p=0.394
	FU1	1.00 (0.25,2.00)	1.00 (0.38,2.50)	1.25 (0.25,2.75)	0.75 (0.25,1.75)	0.75 (0,1.75)	ns p=0.164
	FU2	1.00 (0.19,2.00)	1.00)0.25,2.75)	1.25 (0.25,2.25)	0.75 (0,1.75)	1.00 (0,1.88)	ns p=0.511
MPI – Solicitous response	Start	2.66 (1.50,3.87)	2.83 (1.45,3.63)	2.66 (1.77,4.37)	2.66 (1.50,3.83)	2.50 (1.30,3.83)	ns p=0.929
	Finish	2.66 (1.33,3.83)	2.50 (1.30,4.00)	2.66 (1.33,4.50)	2.66 (1.50,4.08)	2.50 (1.08,3.50)	ns p=0.798
	FU1	2.66 (1.50,4.00)	2.50 (1.66,4.08)	2.83 (1.66,4.50)	2.66 (1.33,4.00)	2.66 (1.50,3.83)	ns p=0.798
	FU2	2.66 (1.50,4.00)	2.42 (1.50,3.50)	2.66 (1.66,4.50)	2.66 (1.50,4.00)	2.50 (1.50,3.75)	ns p=0.704

MPI	Study	All groups	Group 1	Group 2	Group 3	Group 4	Sig.
MPI – Distracting response	Start	1.75 (0.75,2.75)	2.00 (0.75,2.75)	1.50 (0.75,3.00)	2.00 (0.75,2.75)	1.75 (0.50,3.00)	ns p=0.959
	Finish	1.75 (0.75,3.00)	2.00 (0.75,2.75)	1.50 (0.75,2.75)	1.75 (0.75,2.88)	1.75 (0.63,3.00)	ns p=0.927
	FU1	1.75 (0.75,2.75)	1.75 (1.00,2.75)	1.50 (0.75,3.25)	1.75 (0.50,2.75)	2.00 (0.88,3.00)	ns p=0.938
	FU2	1.75 (0.75,3.00)	1.75 (0.75,2.56)	1.50 (0.81,2.75)	1.75 (0.75,3.00)	2.00 (0.75,3.25)	ns p=0.984
Frequency of participation in							
MPI – Household chores	Start	4.80 (3.60,5.60)	4.80 (3.60,5.60)	4.80 (3.35,5.80)	4.60 (3.40,5.55)	4.80 (3.80,5.40)	ns p=0.961
	Finish	4.60 (3.60,5.60)	4.60 (4.20,5.40)	4.40 (3.40,5.60)	4.60 (3.80,5.55)	4.60 (3.60,5.60)	ns p=0.903
	FU1	4.80 (3.60,5.60)	5.00 (4.00,5.60)	5.00 (3.40,5.60)	4.80 (3.65,5.60)	4.80 (3.80,5.40)	ns p=0.852
	FU2	4.80 (3.60,5.60)	4.60 (3.40,5.60)	4.60 (3.40,5.40)	4.80 (3.80,5.70)	4.80 (3.60,5.60)	ns p=0.806
MPI – Outdoor work	Start	2.00 (1.00,3.00)	2.00 (1.30,3.00)	2.00 (0.88,3.10)	2.00 (0.95,3.00)	2.00 (0.85,3.00)	ns p=0.749
	Finish	2.00 (1.00,3.00)	1.78 (1.29,3.00)	2.00 (1.00,3.00)	1.80 (0.85,2.60)	2.00 (0.95,3.05)	ns p=0.687
	FU1	2.00 (1.00,3.00)	2.00 (1.24,2.76)	2.00 (1.00,3.20)	2.00 (0.78,3.00)	2.00 (1.15,3.00)	ns p=0.898
	FU2	2.00 (1.20,3.00)	2.00 (1.40,3.25)	2.00 (1.00,3.00)	2.00 (1.00,2.80)	2.00 (1.15,3.20)	ns p=0.496
MPI – Activities away from home	Start	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.75 (2.75,4.50)	3.25 (2.25,4.25)	3.50 (2.50,4.50)	ns p=0.714
	Finish	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.38 (2.50,4.31)	ns p=0.891
	FU1	3.50 (2.75,4.25)	3.50 (2.75,4.50)	3.50 (2.75,4.00)	3.38 (2.81,4.19)	3.50 (2.44,4.25)	ns p=0.913
	FU2	3.50 (2.50,4.25)	3.50 (2.75,4.50)	3.50 (2.50,4.25)	3.25 (2.63,4.13)	3.25 (2.25,4.50)	ns p=0.923
MPI – Social activities	Start	3.00 (2.30,4.00)	2.75 (2.25,3.75)	3.25 (2.50,4.00)	3.00 (2.33,3.75)	3.38 (2.00,4.06)	ns p=0.655
	Finish	3.25 (2.30,3.75)	3.00 (2.25,4.00)	3.25 (2.50,4.00)	3.13 (2.33,3.75)	3.29 (2.19,4.00)	ns p=0.498
	FU1	3.00 (2.33,3.75)	3.00 (2.33,3.66)	3.00 (2.50,3.75)	3.00 (2.25,3.75)	3.00 (2.25,3.81)	ns p=0.740
	FU2	3.00 (2.32,3.75)	3.00 (2.25,3.75)	3.25 (2.75,3.75)	3.00 (2.13,3.75)	3.00 (2.19,4.00)	ns p=0.362
MPI – General activity level	Start	3.38 (2.75,3.91)	3.40 (2.80,3.88)	3.44 (2.68,3.84)	3.31 (2.50,3.79)	3.34 (2.80,4.05)	ns p=0.901
	Finish	3.31 (2.76,3.81)	3.38 (2.69,3.89)	3.34 (2.84,3.83)	3.30 (2.72,3.71)	3.25 (2.83,3.81)	ns p=0.969
	FU1	3.37 (2.80,3.80)	3.39 (2.88,3.87)	3.46 (2.81,3.78)	3.25 (2.80,3.93)	3.34 (2.70,3.79)	ns p=0.807
	FU2	3.34 (2.73,3.87)	3.38 (2.80,3.98)	3.43 (2.73,3.69)	3.30 (2.67,3.89)	3.30 (2.71,3.86)	ns p=0.904

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Kruskall Wallice not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p< 0.001$

Start = Baseline
Finish = End three months treatment
FU1 = Follow-up 1 (six months)
FU2 = Follow-up 2 (nine months)

Table 79: Multidimensional pain inventory (MPI) A comparison of median scores (25th,75th percentiles) (Imputation analysis)

MPI	Study	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Sig.
Patients perspective of pain							
MPI - Severity	Rx end	2.33 (1.30,3.66) ***	2.60 (1.30,4.00)**	2.33 (1.33,3.66) ***	2.00 (0.66,3.00) ***	2.33 (1.33,3.75) *	p=0.298
	FU1	2.33 (1.30,3.37)	2.33 (1.33,4.00)	2.33 (1.33,3.33)	2.00 (0.66,3.00)	2.33 (1.00,4.00)	p=0.406
	FU2	2.00 (1.00,3.66) ***	2.00 (1.00,4.00)	2.33 (1.00,3.60)	1.63 (0.58,2.66) **	2.15 (0.92,3.75)	p=0.130
		***	ns (p=0.146)	ns (p=0.110)	***	ns (p=0.150)	
MPI - Interference	Rx end	1.05 (0.36,2.38) ***	1.30 (0.36,2.72) ***	1.16 (0.54,2.54) ***	0.90 (0.29,2.27) *	1.00 (0.43,2.40)	p=0.684
	FU1	1.00(0.36,2.32) *	1.09 (0.55,2.73)	0.82 (0.36,2.54) *	0.85 (0.18,2.18) **	1.00 (0.43,2.50)	p=0.350
	FU2	0.95(0.27,2.21) ***	0.90 (0.30,2.72) *	0.90 (0.36,2.00) **	0.58 (0.90,2.19) **	1.09 (0.27,2.40)	p=0.532
		***	* (p=0.047)	*(p=0.033)	***	ns (p=0.336)	
MPI – Life control	Rx end	3.50 (2.50,4.25) ***	3.50 (2.75,4.50) **	3.50 (2.50,4.00)	3.50 (2.50,4.25)	3.50 (2.50,4.25)	p=0.952
	FU1	3.50 (2.50,4.25)	3.50 (2.50,4.50)	3.75 (2.75,4.25)	3.25 (2.50,4.25)	3.50 (2.50,4.56)	p=0.746
	FU2	3.50 (2.75,4.50)	3.50 (2.75,4.50)	3.75 (3.00,4.25)	3.50 (2.75,4.25)	3.50 (2.50,4.75)	p=0.909
		ns (p=0.127)	ns (p=0.992)	ns (p=0.646)	ns (p=0.338)	ns (p=0.211)	
MPI – Affective distress	Rx end	3.00 (2.00,4.00) ***	3.30 (2.00,4.00) **	3.33 (2.00,4.00) **	3.00 (1.92,4.00)	2.83 (2.00,3.62) *	p=0.590
	FU1	3.00 (2.00,3.66)	3.00 (1.66,4.00)	3.00 (2.00,4.00)	3.00 (1.65,4.00)	3.00 (1.66,3.60)	p=0.551
	FU2	3.00 (1.92,4.00)	3.00 (1.66,4.00)	3.33 (2.30,4.00)	3.00 (1.60,4.00)	2.66 (1.60,3.40)	p=0.257
		ns (p=0.406)	ns (p=0.717)	ns (p=0.118)	ns (p=0.529)	ns (p=0.211)	
Response of significant other							
MPI – Support response	Rx end	3.33 (2.32,4.33)	3.33 (2.33,4.33)	3.33 (2.33,5.00)	3.00 (1.70,4.00)	3.60 (2.17,4.47)	p=0.300
	FU1	3.33 (2.00,4.33)	3.33 (2.00,4.33)	3.33 (1.83,4.66)	3.00 (1.83,4.00)	3.33 (2.33,4.00)	p=0.491
	FU2	3.00 (2.00,4.33)	3.00 (2.00,4.33)	3.66 (2.32,4.66)	3.00 (1.60,4.00)	3.15 (2.00,4.31)	p=0.103
MPI – Punishing response	Rx end	1.00 (0,2.00)	1.00 (0,2.5)	1.25 (0.25,2.00)	1.00 (0,2.00)	1.00 (0,1.75)	p=0.394
	FU1	1.00 (0.25,2.00)	1.00 (0.38,2.50)	1.25 (0.25,2.75)	0.75 (0.25,1.75)	0.75 (0,1.75)	p=0.164
	FU2	1.00 (0.19,2.00)	1.00)0.25,2.75)	1.25 (0.25,2.25)	0.75 (0,1.75)	1.00 (0,1.88)	p=0.511
MPI – Solicitous response	Rx end	2.66 (1.33,3.83)	2.50 (1.30,4.00)	2.66 (1.33,4.50)	2.66 (1.50,4.08)	2.50 (1.08,3.50)	p=0.798
	FU1	2.66 (1.50,4.00)	2.50 (1.66,4.08)	2.83 (1.66,4.50)	2.66 (1.33,4.00)	2.66 (1.50,3.83)	p=0.798
	FU2	2.66 (1.50,4.00)	2.42 (1.50,3.50)	2.66 (1.66,4.50)	2.66 (1.50,4.00)	2.50 (1.50,3.75)	p=0.704
MPI – Distracting response	Rx end	1.75 (0.75,3.00)	2.00 (0.75,2.75)	1.50 (0.75,2.75)	1.75 (0.75,2.88)	1.75 (0.63,3.00)	p=0.927
	FU1	1.75 (0.75,2.75)	1.75 (1.00,2.75)	1.50 (0.75,3.25)	1.75 (0.50,2.75)	2.00 (0.88,3.00)	p=0.938
	FU2	1.75 (0.75,3.00)	1.75 (0.75,2.56)	1.50 (0.81,2.75)	1.75 (0.75,3.00)	2.00 (0.75,3.25)	p=0.984
Frequency of participation in							
MPI – Household chores	Rx end	4.60 (3.60,5.60)	4.60 (4.20,5.40)	4.40 (3.40,5.60)	4.60 (3.80,5.55)	4.60 (3.60,5.60)	p=0.903
	FU1	4.80 (3.60,5.60)	5.00 (4.00,5.60)	5.00 (3.40,5.60)	4.80 (3.65,5.60)	4.80 (3.80,5.40)	p=0.852
	FU2	4.80 (3.60,5.60)	4.60 (3.40,5.60)	4.60 (3.40,5.40)	4.80 (3.80,5.70)	4.80 (3.60,5.60)	p=0.806

MPI – Outdoor work	Rx end	2.00 (1.00,3.00)	1.78 (1.29,3.00)	2.00 (1.00,3.00)	1.80 (0.85,2.60)	2.00 (0.95,3.05)	p=0.687
	FU1	2.00 (1.00,3.00)	2.00 (1.24,2.76)	2.00 (1.00,3.20)	2.00 (0.78,3.00)	2.00 (1.15,3.00)	p=0.898
	FU2	2.00 (1.20,3.00)	2.00 (1.40,3.25)	2.00 (1.00,3.00)	2.00 (1.00,2.80)	2.00 (1.15,3.20)	p=0.496
MPI – Activities away from home	Rx end	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.50 (2.75,4.25)	3.38 (2.50,4.31)	p=0.891
	FU1	3.50 (2.75,4.25)	3.50 (2.75,4.50)	3.50 (2.75,4.00)	3.38 (2.81,4.19)	3.50 (2.44,4.25)	p=0.913
	FU2	3.50 (2.50,4.25)	3.50 (2.75,4.50)	3.50 (2.50,4.25)	3.25 (2.63,4.13)	3.25 (2.25,4.50)	p=0.923
MPI – Social activities	Rx end	3.25 (2.30,3.75)	3.00 (2.25,4.00)	3.25 (2.50,4.00)	3.13 (2.33,3.75)	3.29 (2.19,4.00)	p=0.498
	FU1	3.00 (2.33,3.75)	3.00 (2.33,3.66)	3.00 (2.50,3.75)	3.00 (2.25,3.75)	3.00 (2.25,3.81)	p=0.740
	FU2	3.00 (2.32,3.75)	3.00 (2.25,3.75)	3.25 (2.75,3.75)	3.00 (2.13,3.75)	3.00 (2.19,4.00)	p=0.362
MPI – General activity level	Rx end	3.30 (2.76,3.81)	3.38 (2.69,3.89)	3.34 (2.84,3.83)	3.30 (2.72,3.71)	3.25 (2.83,3.81)	p=0.969
	FU1	3.37 (2.80,3.80)	3.39 (2.88,3.87)	3.46 (2.81,3.78)	3.25 (2.80,3.93)	3.34 (2.70,3.79)	p=0.807
	FU2	3.34 (2.73,3.87)	3.38 (2.80,3.98)	3.43 (2.73,3.69)	3.30 (2.67,3.89)	3.30 (2.71,3.86)	p=0.904

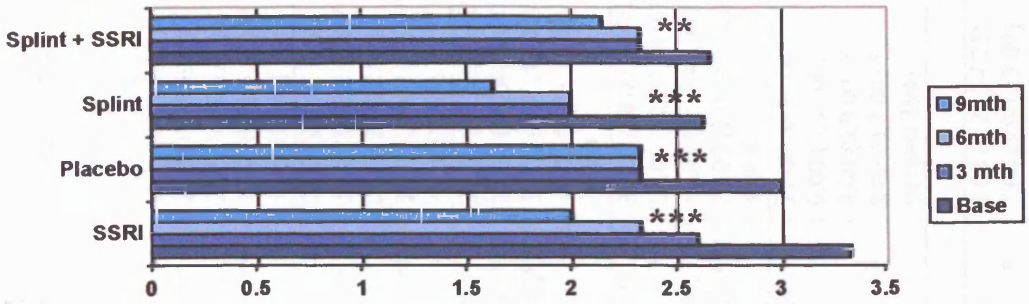
Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Kruskall Wallice not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p< 0.001$

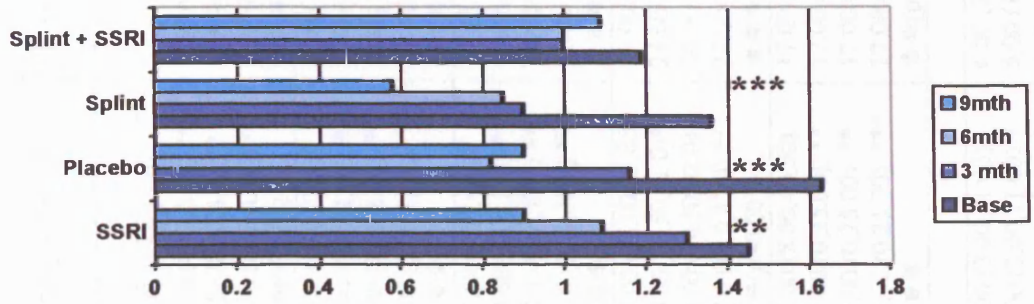
Rx end = End three months treatment
FU1 = Follow-up 1 (six months)
FU2 = Follow-up 2 (nine months)

Figure 70 : Multidimensional pain inventory median scores

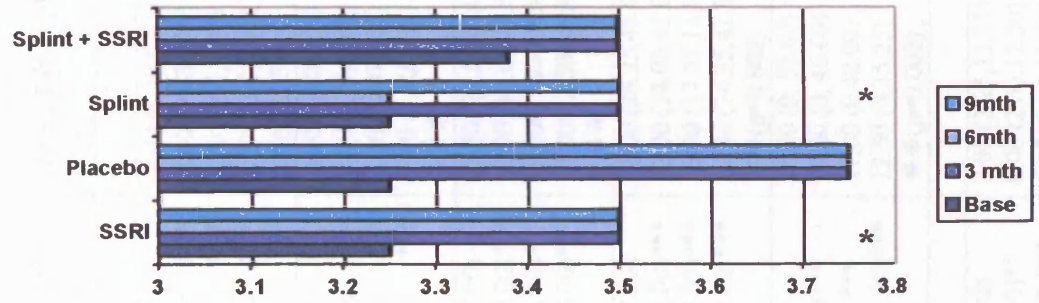
Pain severity



Pain interference



Life control



Affective distress

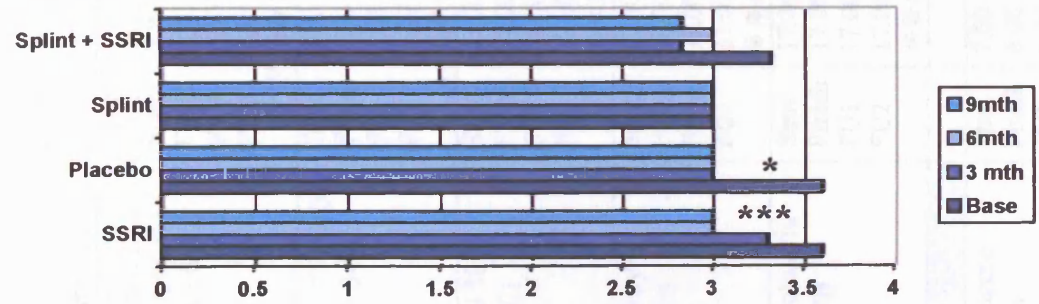


Table 80: McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale. (Imputation analysis)
A comparison of median scores (25th and 75th percentiles)

Self report Questionnaire	Study	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Sig.
MPQ	Time						
Visual analogue scale (VAS) (range 0-10)	Start	2.90 (1.20,5.45)	2.90 (1.20,6.03)	3.30 (1.60,5.60)	2.70 (1.23,4.80)	2.75 (0.90,5.38)	p=0.881
	Finish	2.20 (0.80,4.95) ***	2.40 (0.63,4.90)	2.50 (0.95,5.35) **	2.10 (0.7,4.50) **	2.20 (0.95,5.95)	p=0.682
	FU 1	2.30 (0.60,4.90) ***	1.90 (0.50,4.80) *	2.50 (0.90,4.55) *	2.00 (0.50,4.80) *	2.45 (0.50,6.60)	p=0.506
	FU 2	1.60 (0.50,4.50) ***	1.50 (0.50,4.80) *	2.10 (0.80,4.50)**	0.90 (0.13,3.20) ***	2.30 (0.50,5.35) *	p=0.119
		***	ns (p=0.054)	*(p=0.005)	***	*(p=0.006)	ns
Present pain intensity (PPI) (range 0-5)	Start	2.00 (1.00,2.00)	2.00 (1.00,3.00)	2.00 (1.00,2.00)	2.00 (1.00,2.00)	2.00 (1.00,2.00)	p=0.617
	Finish	1.00 (1.00,2.00) ***	2.00 (1.00,2.00) **	2.00 (1.00,2.00) *	1.00 (1.00,2.00) **	1.00 (1.00,2.00) *	p=0.627
	FU1	1.00 (1.00,2.00) ***	1.00 (1.00,2.00) **	1.00 (1.00,2.00) **	1.00 (1.00,2.00) *	2.00 (1.00,2.00)	p=0.567
	FU2	1.00 (0.50,2.00) ***	1.00 (1.00,2.00) **	1.00 (1.00,2.00) ***	1.00 (0,2.00) ***	1.00 (1.00,2.00) **	p=0.210
		***	***	***	***	*(p=0.005)	ns
MPQ – total % (range 0-100)	Start	31.00 (20.00,47.00)	35.50 (23.50,47.00)	31.00 (19.5,40.0)	30.00 (18.00,39.50)	30.00 (17.50,49.50)	p=0.384
	Finish	27.00 (13.00,40.00)***	29.00 (17.00,45.50) *	29.00 (14.5,37.0)**	24.00 (13.00,31.00)***	20.00 (11.00,42.00) *	p=0.423
	FU1	24.00 (12.00,42.00)***	29.00(15.25,42.50)***	29.0 (13.0,37.0) **	24.00 (16.00,44.00)**	18.00 (9.00,44.00)**	p=0.533
	FU2	22.00 (10.00,38.00)***	27.00(12.50,42.50)***	24.0 (11.0,38.0) ***	22.00 (8.00,36.00) ***	18.00 (7.00,38.00)**	p=0.552
		***	***	***	***	***	ns
MPQ– sensory % (range 0-100)	Start	33.00 (21.00,45.00)	39.00 (26.25,48.00)	31.00 (21.00,45.00)	33.00 (21.00,42.00)	31.50 (18.00,49.00)	p=0.339
	Finish	30.00 (15.00,42.00)***	33.00 (18.00,45.00) *	30.00(17.50,41.0)*	24.00 (15.00,37.50) **	21.00 (12.00,45.00) *	p=0.558
	FU1	27.00 (12.00,42.00)***	33.00 (17.25,14.25) **	27.00 (14.50,42.0)*	30.00 (15.00,39.00) **	18.00 (9.00,45.00) **	p=0.587
	FU2	27.00 (12.00,42.00)***	31.50 (14.25,42.75) **	27.0 (12.0,42.0) **	27.00 (9.00,37.00) ***	21.00 (9.00,47.00) **	p=0.661
		***	**(p=0.002)	**(p=0.001)	***	***	ns
MPQ – affective % (range 0-100)	Start	17.00 (0,42.00)	25.00 (0, 52.00)	17.00 (8.00,40.50)	17.00 (8.00,25.00)	17.00 (0,50.00)	p=0.663
	Finish	17.00 (0, 25.00)***	17.00 (0, 46.00) *	17.00 (0,25.00) **	17.00 (0,25.00) *	9.00 (0,33.00)	p=0.905
	FU1	17.00 (0,33.00) ***	17.00 (0,42.00) *	17.00 (0,25.00) **	17.00 (0,25.00)	8.00 (0,8.00) *	p=0.830
	FU2	17.00 (17.00,25.00)***	12.50 (0,35.25) **	17.00 (0,25.00) ***	17.00 (0,25.00) *	8.00 (0,8.00) *	p=0.903
		***	**(p=0.002)	***	**(p=0.002)	ns (p=0.194)	ns
BDI							
Composite score (range 0-45)	Start	7.00 (3.00,13.00)	7.00 (2.25,13.75)	7.00 (3.00,11.00)	6.00 (2.00,10.50)	8.00 (4.25,14.75)	p=0.344
	Finish	6.00 (3.00,12.00)**	6.00 (2.00.12.50)	7.00 (3.00,11.00) *	5.00 (1.00,10.00) *	7.00 (3.00,13.00)	p=0.106
	FU1	6.00 (2.00,11.00) ***	6.00 (2.00,11.00) **	6.00 (3.00,11.00) *	4.00 (1.00,11.00) *	6.00 (3.00,12.00) *	p=0.435
	FU2	6.00 (2.00,11.00) ***	6.00 (2.00,10.50) ***	5.50 (2.00,10.25) **	4.00 (1.00,10.00) *	7.00 (3.00,13.50)	p=0.121
		***	***	**(p=0.001)	*(p=0.032)	*(p=0.028)	ns

Kellner		All groups	Group 1	Group 2	Group 3	Group 4	Sig.
Illness attitude- total (range 0-30)	Start	8.00 (6.00,11.00)	8.00 (6.00,11.50)	7.00 (6.00,9.50)	7.50 (6.00,11.00)	8.00 (6.00,12.00)	p=0.206
	Finish	7.00 (6.00,11.00)	7.00 (6.00,11.50)	7.00 (6.00,10.00)	7.00 (6.00,10.00)	9.00 (6.00,12.00)	p=0.101
	FU1	8.00 (6.00,10.00)*	7.00 (6.00,11.00)	6.00 (6.00,9.00) *	7.00 (6.00,9.00)	8.00 (6.00,8.00)	p=0.077
	FU2	7.00 (6.00,10.00)***	6.00 (6.00,11.00) **	6.00 (6.00,9.00) *	7.00 (6.00,10.00)	8.50 (6.00,11.75)	p=0.122
		✱✱✱	✱✱(p=0.002)	✱(p=0.13)	ns (p=0.08)	ns (p=0.479)	ns
Hypochondriacal beliefs (range 0-15)	Start	3.00 (3.00,6.00)	4.00 (3.00,6.00)	3.00 (3.00,5.00)	3.00 (3.00,6.00)	3.00 (3.00,6.00)	p=0.477
	Finish	3.00 (3.00,5.00) *	3.00 (3.00,5.00) *	3.00 (3.00,5.00)	3.00 (3.00,5.00)	3.50 (3.00,6.00)	p=0.546
	FU1	3.00 (3.00,5.00) **	3.00 (3.00,6.00)	3.00 (3.00,5.00) *	3.00 (3.00,5.00) *	3.00 (3.00,5.00)	p=0.216
	FU2	3.00 (3.00,5.00) ***	3.00 (3.00,5.00) **	3.00 (3.00,5.00) *	3.00 (3.00,5.00) *	4.00 (3.00,6.00)	p=0.169
		✱✱✱	✱(p=0.006)	ns (p=0.56)	ns (p=0.99)	ns (p=0.69)	ns
Disease phobia (range 0-15)	Start	3.00 (3.00,5.00)	3.00 (3.00,5.50)	3.00 (3.00,4.00)	3.00 (3.00,6.00)	4.00 (3.00,7.00)	p=0.112
	Finish	3.00 (3.00,5.00)	3.00 (3.00,5.50)	3.00 (3.00,5.00)	3.00 (3.00,5.25)	5.00 (3.00,6.75)	p=0.068
	FU1	3.00 (3.00,5.00) *	3.00 (3.00,5.00)	3.00 (3.00,4.00)	3.00 (3.00,5.00)	4.00 (3.00,6.00)	p=0.038
	FU2	3.00 (3.00,5.00) *	3.00 (3.00,5.00)	3.00 (3.00,4.00)	3.00 (3.00,5.25)	3.00 (3.00,6.00)	p=0.138
		✱(p=0.02)	ns (p=0.67)	ns (p=0.419)	ns (p=0.129)	ns (p=0.273)	ns

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Kruskall-Wallis not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p<0.001$***

Start = Baseline
Finish = End three months treatment
FU1 = Follow-up 1 (six months)
FU2 = Follow-up 2 (nine months)

Table 81: McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale. (Imputation analysis)

A comparison of median scores (25th and 75th percentiles)

Self report Questionnaire	Study	All groups (n=250)	Group 1 (n=63)	Group 2 (n=63)	Group 3 (n=62)	Group 4 (n=62)	Sig.
MPQ	Time						
Visual analogue scale (VAS)(range 0-10)	Rx end FU 1 FU 2	2.20 (0.80,4.95) *** 2.30 (0.60,4.90) *** 1.60 (0.50,4.50) *** ***	2.40 (0.63,4.90) 1.90 (0.50,4.80) * 1.50 (0.50,4.80) * ns (p=0.054)	2.50 (0.95,5.35) ** 2.50 (0.90,4.55) * 2.10 (0.80,4.50)** *(p=0.005)	2.10 (0.7,4.50) ** 2.00 (0.50,4.80) * 0.90 (0.13,3.20) *** ***	2.20 (0.95,5.95) 2.45 (0.50,6.60) 2.30 (0.50,5.35) * *(p=0.006)	p=0.682 p=0.506 p=0.119 ns
Present pain intensity (PPI)(range 0-5)	Rx end FU1 FU2	1.00 (1.00,2.00) *** 1.00 (1.00,2.00) *** 1.00 (0.50,2.00) *** ***	2.00 (1.00,2.00) ** 1.00 (1.00,2.00) ** 1.00 (1.00,2.00) ** ***	2.00 (1.00,2.00) * 1.00 (1.00,2.00) ** 1.00 (1.00,2.00) *** ***	1.00 (1.00,2.00) ** 1.00 (1.00,2.00) * 1.00 (0,2.00) *** ***	1.00 (1.00,2.00) * 2.00 (1.00,2.00) 1.00 (1.00,2.00) ** *(p=0.005)	p=0.627 p=0.567 p=0.210 ns
MPQ – total % (range 0-100)	Rx end FU1 FU2	27.00 (13.00,40.00)*** 24.00 (12.00,42.00)*** 22.00 (10.00,38.00)*** ***	29.00 (17.00,45.50) * 29.00 (15.25,42.50)*** 27.00 (12.50,42.50)*** ***	29.00 (14.5,37.0)** 29.0 (13.0,37.0) ** 24.0 (11.0,38.0) *** ***	24.00 (13.00,31.00)*** 24.00(16.00,44.00)** 22.00 (8.00,36.00) *** ***	20.00 (11.00,42.00) * 18.00 (9.00,44.00)** 18.00 (7.00,38.00)** ***	p=0.423 p=0.533 p=0.552 ns
MPQ– sensory % (range 0-100)	Rx end FU1 FU2	30.00 (15.00,42.00)*** 27.00 (12.00,42.00)*** 27.00 (12.00,42.00)*** ***	33.00 (18.00,45.00) * 33.00 (17.25,14.25) ** 31.50 (14.25,42.75) ** **(p=0.002)	30.00(17.50,41.0)* 27.00 (14.50,42.0)* 27.0 (12.0,42.0) ** **(p=0.001)	24.00 (15.00,37.50) ** 30.00 (15.00,39.00) ** 27.00 (9.00,37.00) *** ***	21.00 (12.00,45.00) * 18.00 (9.00,45.00) ** 21.00 (9.00,47.00) ** ***	p=0.558 p=0.587 p=0.661 ns
MPQ – affective % (range 0-100)	Rx end FU1 FU2	17.00 (0, 25.00)*** 17.00 (0,33.00) *** 17.00 (17.00,25.00)*** ***	17.00 (0, 46.00) * 17.00 (0,42.00) * 12.50 (0,35.25) ** **(p=0.002)	17.00 (0,25.00) ** 17.00 (0,25.00) ** 17.00 (0,25.00) *** ***	17.00 (0,25.00) * 17.00 (0,25.00) 17.00 (0,25.00) * **(p=0.002)	9.00 (0,33.00) 8.00 (0,8.00) * 8.00 (0,8.00) * ns (p=0.194)	p=0.905 p=0.830 p=0.903 ns
BDI							
Composite score (range 0-45)	Rx end FU1 FU2	6.00 (3.00,12.00)** 6.00 (2.00,11.00) *** 6.00 (2.00,11.00) *** ***	6.00 (2.00.12.50) 6.00 (2.00,11.00) ** 6.00 (2.00,10.50) *** ***	7.00 (3.00,11.00) * 6.00 (3.00,11.00) * 5.50 (2.00,10.25) ** **(p=0.001)	5.00 (1.00,10.00) * 4.00 (1.00,11.00) * 4.00 (1.00,10.00) * *(p=0.032)	7.00 (3.00,13.00) 6.00 (3.00,12.00) * 7.00 (3.00,13.50) *(p=0.028)	p=0.106 p=0.435 p=0.121 ns

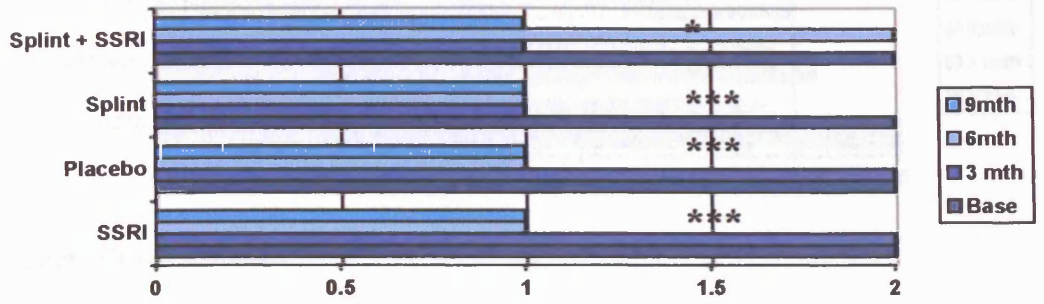
Kellner		All groups	Group 1	Group 2	Group 3	Group 4	
Illness attitude- total (range 0-30)	Rx end FU1 FU2	7.00 (6.00,11.00) 8.00 (6.00,10.00)* 7.00 (6.00,10.00)*** ***	7.00 (6.00,11.50) 7.00 (6.00,11.00) 6.00 (6.00,11.00) ** **(p=0.002)	7.00 (6.00,10.00) 6.00 (6.00,9.00) * 6.00 (6.00,9.00) * *(p=0.13)	7.00 (6.00,10.00) 7.00 (6.00,9.00) 7.00 (6.00,10.00) ns (p=0.08)	9.00 (6.00,12.00) 8.00 (6.00,8.00) 8.50 (6.00,11.75) ns (p=0.479)	p=0.101 p=0.077 p=0.122 ns
Hypochondriacal beliefs (range 0-15)	Rx end FU1 FU2	3.00 (3.00,5.00) * 3.00 (3.00,5.00) ** 3.00 (3.00,5.00) *** ***	3.00 (3.00,5.00) * 3.00 (3.00,6.00) 3.00 (3.00,5.00) ** *(p=0.006)	3.00 (3.00,5.00) 3.00 (3.00,5.00) * 3.00 (3.00,5.00) * ns (p=0.56)	3.00 (3.00,5.00) 3.00 (3.00,5.00) * 3.00 (3.00,5.00) * ns (p=0.99)	3.50 (3.00,6.00) 3.00 (3.00,5.00) 4.00 (3.00,6.00) ns (p=0.69)	p=0.546 p=0.216 p=0.169 ns
Disease phobia (range 0-15)	Rx end FU1 FU2	3.00 (3.00,5.00) 3.00 (3.00,5.00) * 3.00 (3.00,5.00) * *(p=0.02)	3.00 (3.00,5.50) 3.00 (3.00,5.00) 3.00 (3.00,5.00) ns (p=0.67)	3.00 (3.00,5.00) 3.00 (3.00,4.00) 3.00 (3.00,4.00) ns (p=0.419)	3.00 (3.00,5.25) 3.00 (3.00,5.00) 3.00 (3.00,5.25) ns (p=0.129)	5.00 (3.00,6.75) 4.00 (3.00,6.00) 3.00 (3.00,6.00) ns (p=0.273)	p=0.068 p=0.038 p=0.138 ns

Group 1 – Fluoxetine medication
Group 2 – Placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy
Kruskall-Wallis not significant between groups
Wilcoxon significance $p<0.05$ *, $p<0.005$ **, $p<0.001$***

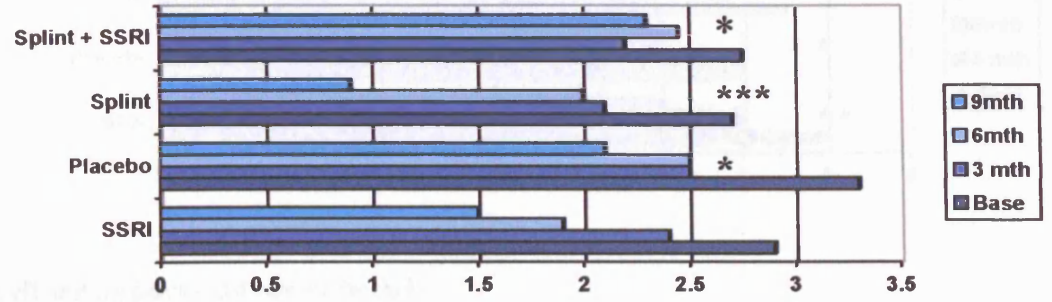
Rx end = End three months treatment
FU1 = Follow-up 1 (six months)
FU2 = Follow-up 2 (nine months)

Figure 71: McGill pain questionnaire, Kellner illness attitude BDI median scores

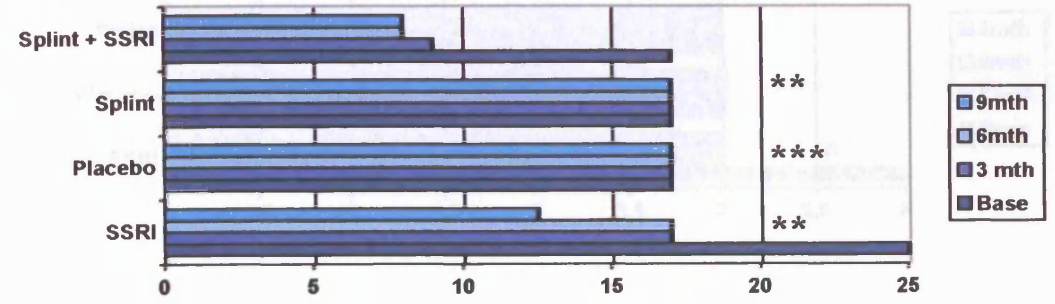
Present pain intensity



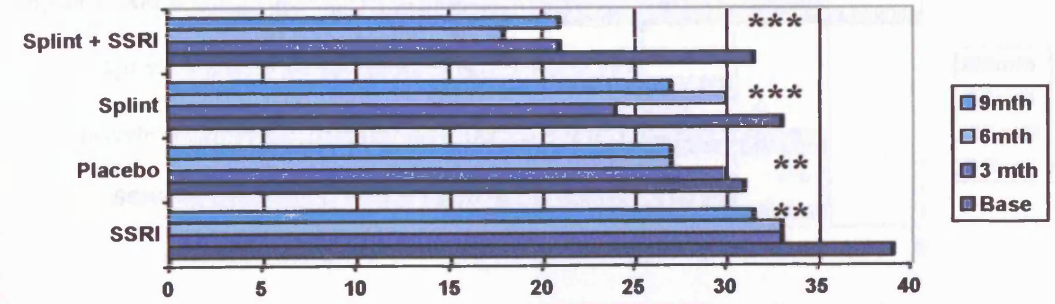
Visual analogue scale



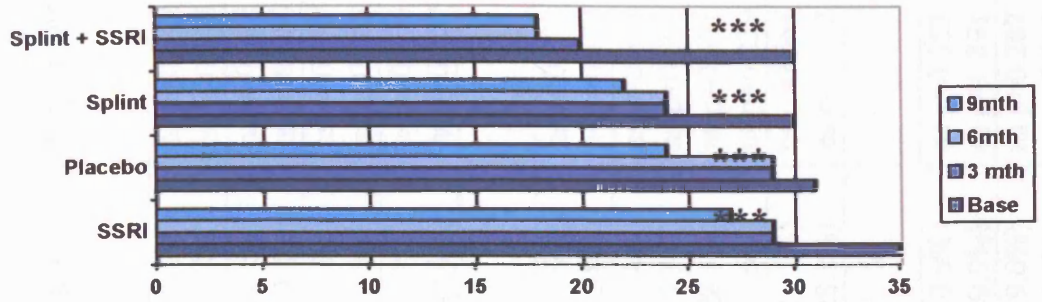
MPQ – affective



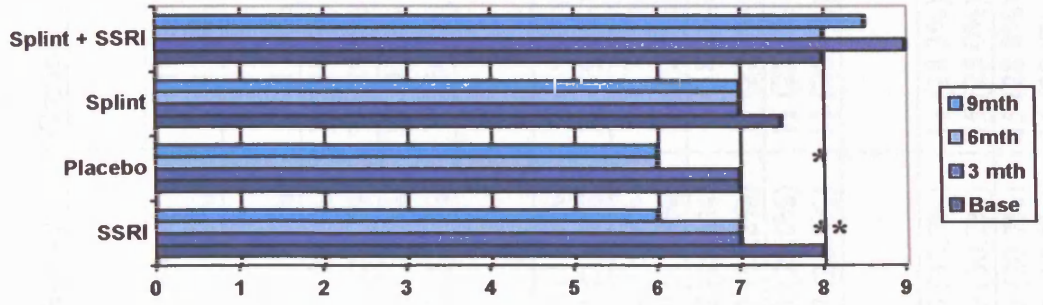
MPQ – sensory



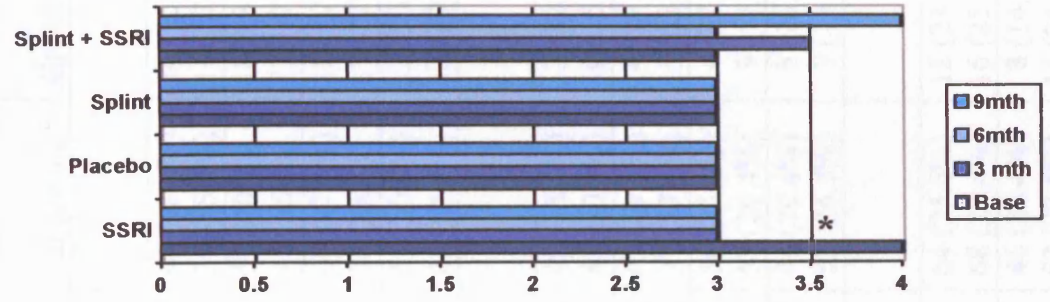
MPQ – total



Kellner illness attitude



Kellner hypochondriacal beliefs



Beck depression index

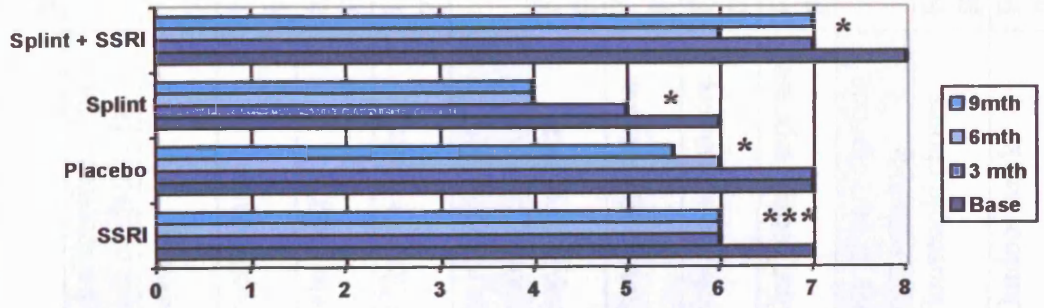


Table 82: **Relapse in scores since end of treatment** number of subjects and (%) N=250
Multidimensional pain inventory (MPI)

MPI	Study	All groups	Group 1	Group 2	Group 3	Group 4	Significance
Patients perspective of pain and impact on daily life	Time						
MPI - Severity	Follow-up 1	46 (18.4%)	10 (15.9%)	12 (19%)	12 (19.4%)	12 (19.4%)	ns p=0.948
	Follow-up 2	39 (15.6%)	11 (17.5%)	9 (14.3%)	7 (11.3%)	12 (19.4%)	ns p=0.618
MPI - Interference	Follow-up 1	50 (20%)	18 (28.6%)	12 (19%)	6 (9.7%)	14 (22.6%)	ns p=0.062
	Follow-up 2	40 (16%)	11 (17.5%)	10 (15.9%)	7 (11.3%)	12 (19.4%)	ns p=0.650
MPI – Life control	Follow-up 1	69 (27.6%)	12 (19%)	16 (25.4%)	19 (30.6%)	22 (35.5%)	ns p=0.197
	Follow-up 2	70 (28%)	17 (27%)	17 (27.0%)	18 (29.0%)	18 (29.0%)	ns p=0.988
MPI – Affective distress	Follow-up 1	51 (20.4%)	13 (20.6%)	14 (22.2%)	13 (21.0%)	11 (17.7%)	ns p=0.938
	Follow-up 2	62 (24.8%)	13 (20.6%)	22 (34.9%)	15 (24.2%)	12 (19.4%)	ns p=0.169
Response of significant other person to patient							
MPI – Support response	Follow-up 1	42 (18.0%)	13 (22.0%)	7 (11.5%)	8 (14.3%)	14 (24.6%)	ns p=0.204
	Follow-up 2	47 (20.2%)	10 (16.9%)	13 (21.3%)	11 (19.6%)	13 (22.8%)	ns p=0.872
MPI – Punishing response	Follow-up 1	41 (19.0%)	14 (27.5%)	10 (16.9%)	8 (16.3%)	9 (15.8%)	ns p=0.371
	Follow-up 2	37 (17.1%)	11 (21.6%)	9 (15.3%)	6 (12.2%)	11 (19.3%)	ns p=0.601
MPI – Solicitous response	Follow-up 1	56 (25.9%)	14 (27.5%)	17 (28.8%)	9 (18.4%)	16 (28.1%)	ns p=0.591
	Follow-up 2	57 (26.4%)	9 (17.6%)	19 (32.2%)	11 (22.4%)	18 (31.6%)	ns p=0.239
MPI – Distracting response	Follow-up 1	44 (20.4%)	8 (15.7%)	13 (22.0%)	11 (22.4%)	12 (21.1%)	ns p=0.861
	Follow-up 2	53 (24.5%)	7 (13.7%)	17 (28.8%)	13 (26.5%)	16 (28.1%)	ns p=0.232
Frequency of participation in common activities							
MPI – Household chores	Follow-up 1	64 (25.6%)	15 (23.8%)	19 (30.2%)	11 (18.3%)	19 (30.6%)	ns p=0.353
	Follow-up 2	68 (27.4%)	16 (25.4%)	19 (30.2%)	15 (25.0%)	18 (29.0%)	ns p=0.891
MPI – Outdoor work	Follow-up 1	46 (20.4%)	8 (14.0%)	12 (20.7%)	15 (28.8%)	11 (19.0%)	ns p=0.287
	Follow-up 2	53 (23.5%)	14 (24.1%)	10 (17.2%)	16 (30.8%)	13 (22.4%)	ns p=0.416
MPI – Activities away from home	Follow-up 1	54 (21.8%)	16 (25.4%)	11 (17.5%)	13 (21.7%)	14 (22.6%)	ns p=0.754
	Follow-up 2	51 (20.6%)	15 (23.8%)	11 (17.5%)	15 (25.0%)	10 (16.1%)	ns p=0.523

Self report Questionnaire	Study	All groups	Group 1	Group 2	Group 3	Group 4	
MPI – Social activity level	Follow-up 1	50(20.0%)	14(22.2%)	9 (14.3%)	11 (17.7%)	16 (25.8%)	ns p=0.404
	Follow-up 2	60(24.0%)	14 (22.2%)	17 (27.0%)	16 (25.8%)	13 (21.0%)	ns p=0.790
MPI – General activity level	Follow-up 1	67 (27.0%)	16 (25.4%)	15 (23.8%)	20 (33.3%)	16 (25.8%)	ns p=0.643
	Follow-up 2	70 (28.2%)	19 (30.2%)	16 (25.4%)	18 (29.0%)	17 (27.4%)	ns p=0.924

McGill pain questionnaire (MPQ), Beck depression index (BDI) and Kellner illness attitude scale.(Kellner)

MPQ	Time						
Visual analogue scale	Follow-up 1	48 (21.0%)	11 (19.6%)	9 (15.8%)	14 (23.7%)	14 (24.6%)	ns p=0.637
(VAS)(range 0-10)	Follow-up 2	39 (17.0%)	13 (23.2%)	11 (19.3%)	5 (8.5%)	10 (17.5%)	ns p=0.188
Present pain intensity (PPI)	Follow-up 1	28 (11.5%)	5 (8.2%)	8 (12.7%)	9 (15.3%)	6 (9.8%)	ns p=0.631
(range 0-5)	Follow-up 2	24 (9.8%)	8 (13.1%)	6 (9.5%)	5 (8.5%)	5 (8.2%)	ns p=0.788
MPQ – total %	Follow-up 1	42 (17.9%)	11 (19.3%)	11 (18.0%)	14 (24.1%)	6 (10.2%)	ns p=0.260
(range 0-100)	Follow-up 2	39 (16.6%)	11 (19.3%)	11 (18.0%)	8 (13.8%)	9 (15.3%)	ns p=0.850
MPQ– sensory %	Follow-up 1	39 (16.6%)	11 (19.3%)	9 (14.8%)	14 (24.1%)	5 (8.5%)	ns p=0.130
(range 0-100)	Follow-up 2	39 (16.6%)	12 (21.1%)	10 (16.4%)	9 (15.5%)	8 (13.6%)	ns p=0.738
MPQ – affective %	Follow-up 1	37 (15.7%)	10 (17.5%)	9 (14.8%)	12 (20.7%)	6 (10.2%)	ns p=0.451
(range 0-100)	Follow-up 2	30 (12.8%)	9 (15.8%)	7 (11.5%)	7 (12.1%)	7 (11.9%)	ns p=0.890
BDI							
Composite score	Follow-up 1	43 (17.7%)	6 (9.8%)	15 (24.2%)	11 (18.6%)	11 (18.0%)	ns p=0.291
(range 0-45)	Follow-up 2	42 (17.3%)	9 (14.8%)	9 (14.5%)	10 (16.9%)	14 (23.0%)	ns p=0.577
Kellner							
Illness attitude- total	Follow-up 1	29 (11.8%)	9 (14.8%)	3 (4.8%)	10 (16.4%)	7 (11.7%)	ns p=0.192
(range 0-30)	Follow-up 2	31 (12.7%)	4 (6.6%)	4 (6.3%)	12 (19.7%)	11 (18.3%)	ns p=0.032
Hypochondriacal beliefs	Follow-up 1	25 (10.2%)	7 (11.3%)	4 (6.3%)	8 (13.1%)	6 (10.0%)	ns p=0.643
(range 0-15)	Follow-up 2	28 (11.4%)	4 (6.5%)	5 (7.9%)	10 (16.4%)	9 (15.0%)	ns p=0.209
Disease phobia	Follow-up 1	19 (7.7%)	5 (8.2%)	3 (4.8%)	3 (4.8%)	8 (13.3%)	ns p=0.244
(range 0-15)	Follow-up 2	17 (6.9%)	3 (4.9%)	3 (4.8%)	5 (8.1%)	6 (10.0%)	ns p=0.605

Group 1 – Fluoxetine medication Group 3 – Splint therapy

Group 2 – Placebo medication Group 4 – Fluoxetine and splint therapy

Intra group analysis :Repeated measures ANOVA : $p<0.05$ * $p<0.005$ ** $p<0.001$*** Inter group anaysis : Chi squared (not significant)

Figure 72a: MPI – severity (FU-1, 6 months) relapse since treatment end.

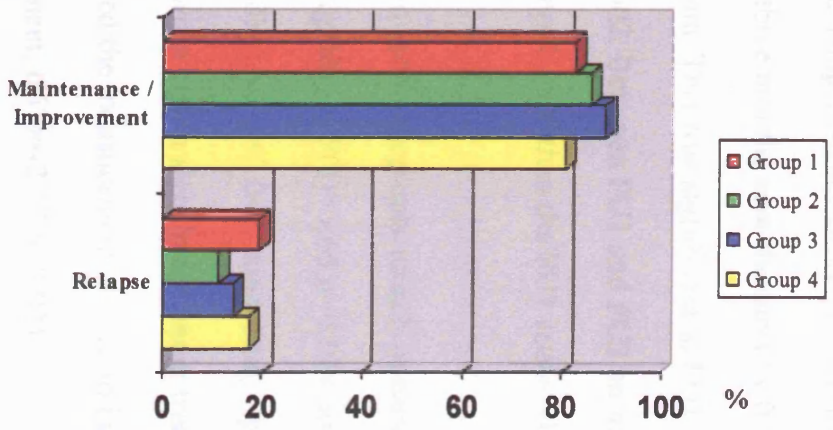


Figure 72b: MPI – severity (FU-2, 9 months) relapse since treatment end

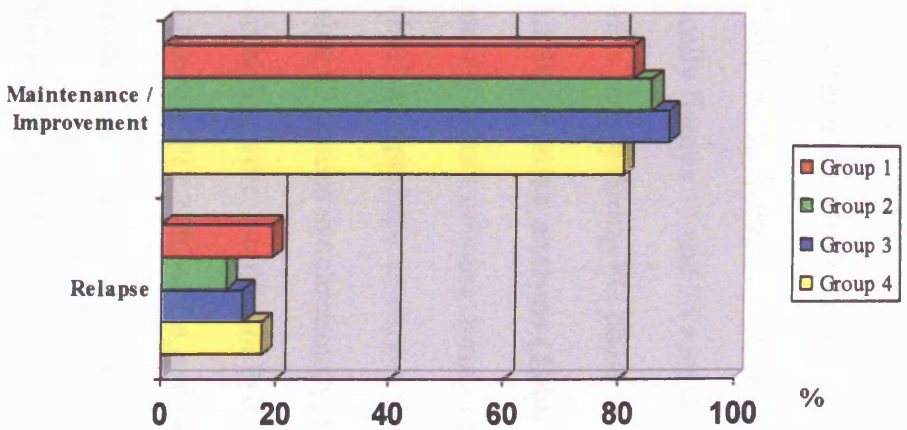


Figure 73a: MPQ-VAS (FU-1, 6 months) relapse since treatment end

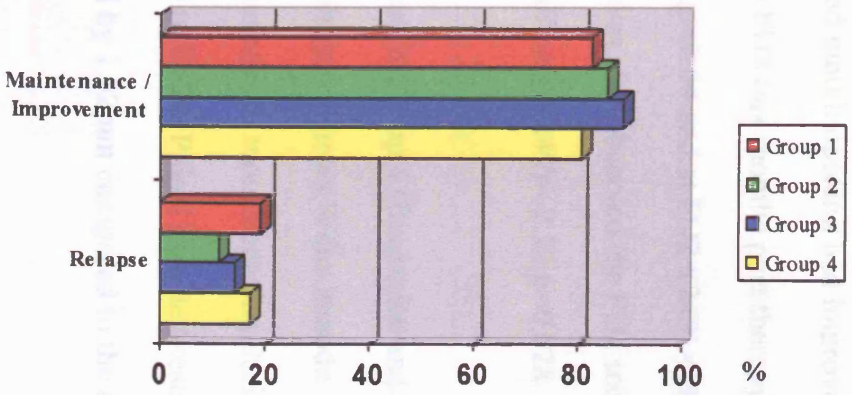
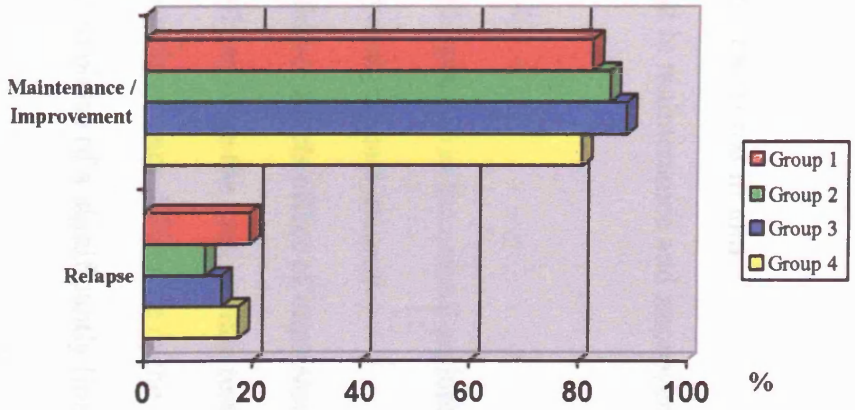


Figure 73b: MPQ-VAS (FU-2, 9 months) relapse since treatment end



9.2.4 Clinical outcome measures

9.2.4.1 Interincisal mouth opening mean (+/- SD) measured in mm

Graphically figures 74 and 75 reveal the clear trend in maintenance and improvement in mouth opening during FU phase.

9.2.4.1.1 Imputation analysis (Table 83,figure 74)

In summary, mouth opening during follow-up had improved in the overall patient cohort by 1mm, perhaps an almost imperceptible yet significant amount.

Analysing all groups synchronously, the GLM within-subjects effect of improved mouth opening were significant $F(2)=6.87, p=0.001$, as were the multivariate tests Wilk's lambda, $F(2,248) =5.04, p=0.007$, suggesting significant difference in the measurement of mouth opening during the follow-up phase of a significantly linear trend $F(1)=9.57, p=0.002$.

Paired sample t-tests for all groups together, showed mouth opening had improved at FU1(three months post therapy) by 0.57mm and at FU2 (six months post therapy) by 0.99mm. This was significant at FU1 $t(249)=-2.05, p=0.04$ and at FU2 $t(249) =-3.09$, $p=0.002$. Between FU1 and FU2 an improvement was also observed the FU2 score 0.42mm higher than the FU1 score which was significant $t(249)=-2.21, p=0.028$.

Within each group only mouth opening improvement in group 4 (fluoxetine and splint) was significant $F(2)=3.68, p=0.028$, as were the multivariate tests Wilks lambda $F(2,60)=3.36$, $p=0.041$, suggesting significant differences in mouth opening during follow-up with a significant linear trend, $F(1),5.60, p=0.021$. Paired sample t-tests showed the measurement at FU2 to have increased by 1.52mm compared to the end of treatment, $t(61)=-2.37, p=0.021$.

However, inter group analysis, using the parametric one-way ANOVA, revealed no significant difference in mouth opening improvement during the follow-up phase between groups.

9.2.4.1.2 Completers analysis (Table 84, figure 75)

Mouth opening during follow-up, amongst the FU completers, had improved by 1.23mm similar to the imputation analysis. Analysing all groups synchronously, the repeated measures ANOVA of within subjects effect were significant $F(2)= 6.5$, $p=0.002$ as were the multivariate tests, Wilk's lambda, $F(2,136)= 4.8$, $p= 0.009$, suggesting significant difference in the measurement of mouth opening during follow-up phase of a significantly linear trend $F(1,137)= 9.2, p= 0.003$.

Paired sample t-tests for all groups together showed mouth opening had improved at FU1 (three months post therapy) by 0.38mm and at FU2 (six months post therapy) by 1.23mm. This was not statistically significant at FU1,$p=0.08$ but did reach significance at FU2 $t =(138)$, $p=0.031$. Between FU1 and FU2 an improvement was also observed, the FU2 score was 0.85mm higher than the FU1 score which was significant $t(249)$ $p=0.004$. For each individual group intra and inter group analysis was not significant.

9.2.4.2 <u>Relapse in measured mouth opening during follow-up</u> (Table 85)

Although intra group McNemar analysis suggests there was a significant element of relapse between FU1 and FU2, notably in groups 2 and 3, the non parametric intergroup χ^2 analysis revealed no significant difference in relapse between groups at either FU1 ($p=0.651$) or FU2 ($p=0.858$).

Table 83 : Interincisal mouth opening mean (+/- SD) Imputation analysis

Time	All groups	Group1 n=63	Group2 n=63	Group3 n=62	Group4 n=62	One-way ANOVA
End treatment 3/12	40.28 (9.52)	39.67 (10.18)	40.52 (9.45)	41.60 (8.18)	39.34 (10.17)	ns p=0.55
Follow-up 1 6/12 (FU1)	40.85 (9.40) * p=0.04	40.65 (10.31)	40.62 (9.26)	41.90 (8.32)	40.23 (9.70) ns p=0.169	ns p=0.78
Follow-up 2 9/12 (FU2)	41.27 (9.45) **p=0.002	40.83 (10.04)	41.21 (9.54)	42.19 (8.74)	40.85 (9.60) * p=0.021	ns p=0.84
	** p=0.001	ns p=0.061	ns p=0.337	ns p=0.572	* p=0.028	

Table 84 : Interincisal mouth opening mean (+/- SD) Completers analysis

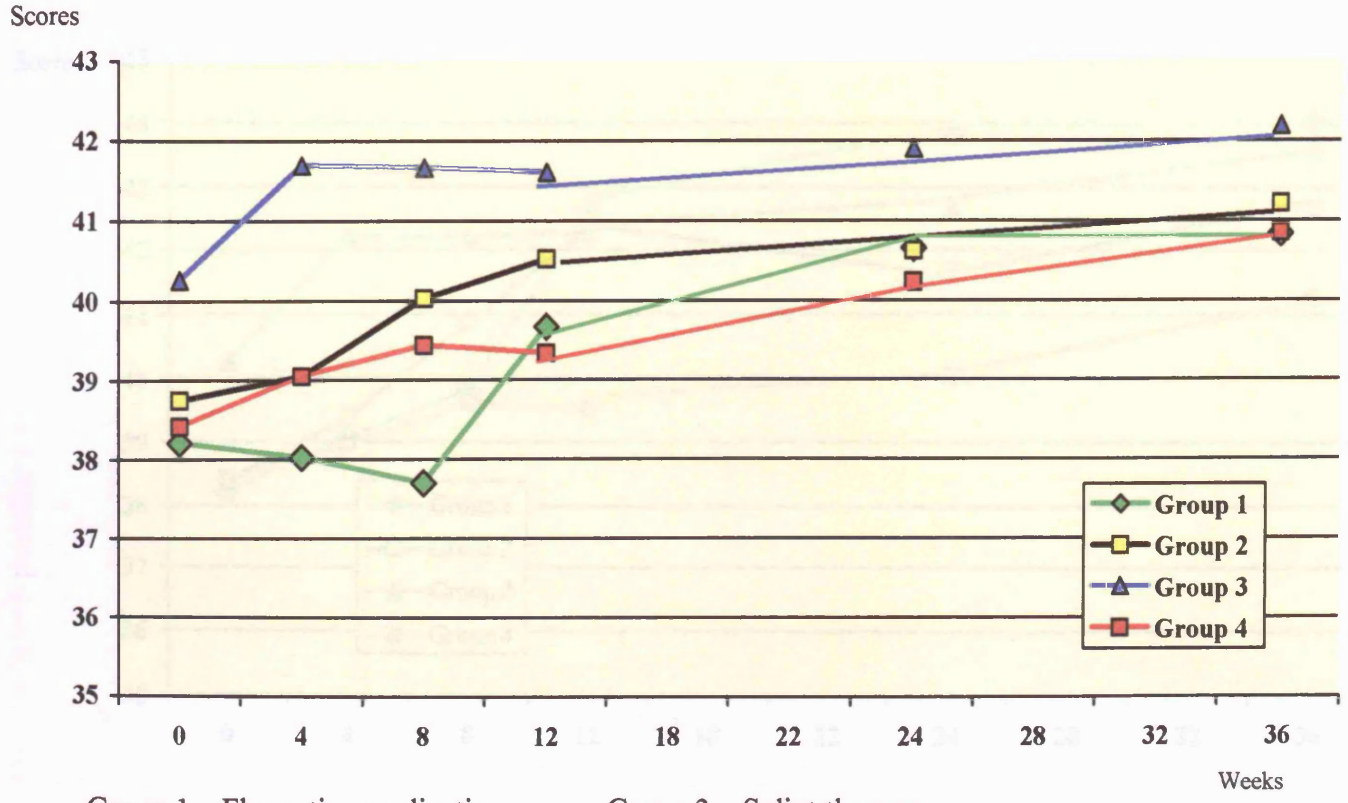
Time	All groups	Group1	Group2	Group3	Group4	One-way ANOVA
End treatment 3/12	n=165 41.62 (9.22)	n=38 42.66 (9.73)	n=42 42.36 (8.71)	n=40 42.28 (8.32)	n=45 39.49 (9.93)	ns p=0.342
Follow-up 1 6/12 (FU1)	n=145 42.00 (8.66) ns p=0.088	n=34 43.85 (8.12)	n=36 41.69 (9.43)	n=36 42.69 (8.54)	n=39 40.03 (8.40)	ns p=0.279
Follow-up 2 9/12 (FU2)	n=139 42.85 (8.74) * p=0.031	n=33 44.00 (7.35)	n=36 42.67 (9.80)	n=34 43.62 (9.15)	n=36 41.25 (8.50)	ns p=0.565
	* p=0.005	ns p=0.065	ns p=0.219	ns p=0.842	ns p=0.085	

Table 85 : Relapse in measured mouth opening during follow-up numbers (%)

Time	All groups	Group 1	Group2	Group3	Group4	Significance
FU1	63 (29.4%) (n=214)	19 (33.3%) (n=57)	14 (26.4%) (n=53)	13 (24.5%) (n=53)	17 (33.3%) (n=51)	ns p=0.211
FU2	80 (37.7%) (n=212)	20 (37%) (n=54)	18 (35.3%) (n=51)	19 (35.8%) (n=53)	23 (42.6%) (n=54)	ns p=0.102
	***p<0.001	ns (p=0.25)	*p=0.031	*p=0.031	ns (p=0.25)	

Figure 74: Interincisal mouth opening
A comparison of mean scores showing maintenance and continued improvement in scores during follow-up.

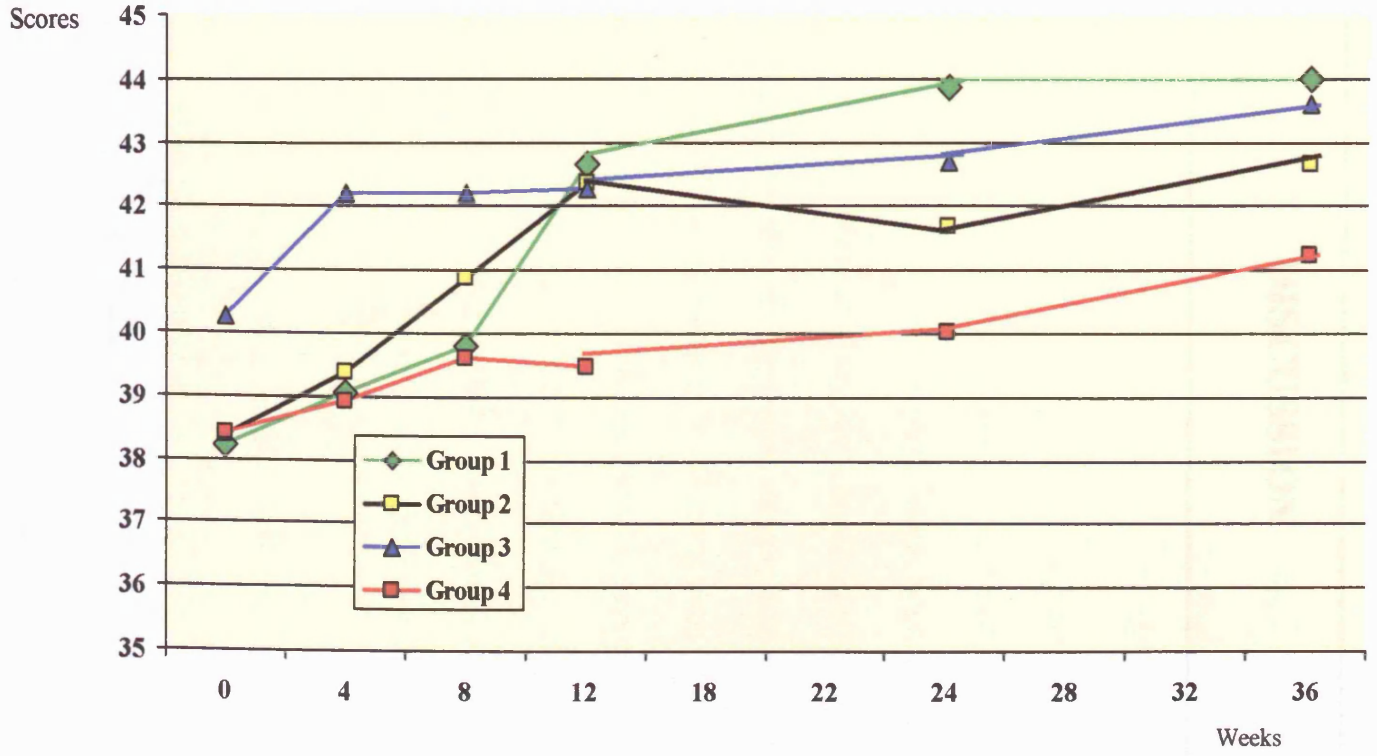
Imputation analysis showing three month (week 12) treatment and follow-up at six months (week 24) and nine months (week36).



Group 1 – Fluoxetine medication
Group 2 – placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

Figure 75: Interincisal mouth opening
A comparison of mean scores showing maintenance and continued improvement in scores during follow-up.

Completers analysis showing three month (week 12) treatment and follow-up at six months (week 24) and nine months (week36).



Group 1 – Fluoxetine medication
Group 2 – placebo medication
Group 3 – Splint therapy
Group 4 – Fluoxetine and splint therapy

IX DISCUSSION

Hypothesis (7): The four therapeutic groups were equally adherent to therapy.

9.3 Adherence and maintenance within treatment and follow-up

Adherence synonymous with the term compliance indicates the extent to which patients follow the instructions for prescribed treatment and is considered a non-judgemental statement of patient, prescriber and treatment, (Haynes et al,2006). Adherence to therapy is essential in assessing treatment efficacy and safety, (Shaya,2005, Formica et al,2004).Generally however, adherence rates are low with many patients showing resistance to taking medical therapy, (Pound,2005).It has been reported that patients prescribed self-administered medication take less than 50% of the prescribed dosage, (WHO 2003, Haynes et al 2006).

Non-adherence may arise for various reasons, frequently related to inadequate, misunderstood or poor memory recall of treatment instructions and patient concern over the actual need for treatment and the feared or experienced adverse effects of treatment, (Houston et al,1997).Clinicians are sometimes reluctant to discuss side effects of treatment, nevertheless, explaining adverse effects of treatment has not been found to adversely effect adherence,(Haynes et al,2006).This finding is consistent with the accepted provision of patients with clear and adequate information regarding their treatment including expected side effects, (Probert,1996, Zakrzewska et al, 2002).This approach of providing clear and adequate information was followed throughout this RCT comparing medical and physical therapy in TMD.

Individual patient factors including behaviour, personality type, social support, motivation, participation or engagement in activity, age, occupation, socioeconomic status, education and beliefs may have an impact on adherence and require further

investigation, (WHO,2003, White,2005). Granger et al 2005, found patients with high adherence were more likely to be men, less likely to smoke and likely to have more co morbidities. A recent study suggests high levels of independence, predict low levels of adherence to medication and this appears to be related to the element of self reliance, (Insel, 2006).The consequences of poor adherence for an individual may be under-treatment and hence potential decreased benefit of treatment but also an underestimate of side effects, (Haynes et al, 2006).This in turn causes problems for the clinician in determining the appropriate dosage and assessment of efficacy, (Connor et al,2004).

On a global level non adherence can lead to medication wastage and overall increased health care costs, (Cleemput et al,2002, Shaya,2005). The implication of non-adherence can be profound particularly in the sphere of antimicrobial therapy with respect to patient welfare, incompletely treated infections, the rise of drug resistant strains and ineffective disease management programmes, (Shaya,2005, Vrijens and Urquhart, 2005, Connor et al,2004).

Non adherence may also have serious consequences in life threatening or long term chronic conditions such as heart failure, hypertension, diabetes, HIV and multiple sclerosis, (Granger et al,2005, Hutchinson, 2005, Maggiolo et al,2002, Brown et al 1999).Interestingly, high levels of adherence even if only to placebo were found to be associated with a 35% lower mortality, improved survival, decreased morbidity and decreased admissions to hospital in patients with congestive heart failure, (Granger et al,2005).It was postulated that the reason adherence even to placebo may result in lower mortality might result from a general placebo response to expectations and belief in a particular therapy; adherence acting as a marker for healthier behavioural patterns hence resulting in better outcome (White,2005).

Miller,1997 suggest adherence to be a complex multifactorial behavioural process; reasons for behavioural non-adherence to physical activity, may be different to non-adherence to medication. This could certainly be investigated in TMD comparing adherence to jaw exercises or splint wear and medical therapy. In this particular RCT, adherence did not appear to differ between physical and medical therapy.

Variable adherence to medication may lead to erratic patterns of drug exposure and hence inconsistent clinical response,(Vrijens et al 2005). How outpatients use their prescription drugs is termed 'pharmionics' and is now an essential element of biopharmaceutics together with pharmacokinetics and pharmacodynamics.(Vrijens et al, 2005). Apart form non-adherence, varying times of dosage and hence dosing intervals can effect the steady state of drug levels and assumed pharmacological profile (Vrijens and Goetghebeur, 2004).In order to examine adherence a reliable record of regular dosing frequency and timing of actual drug intake are therefore required, (Haynes et al,2006). Popular indirect measures of adherence including self report and pill counts. These were the simple techniques employed in this RCT. Martenyi et al, 2002, investigating fluoxetine versus placebo in PTSD assessed patient compliance at each visit by counting returned medication and direct questioning. Patients were recorded as noncompliant if they missed more than four consequetive days or more than ten cumulative days of study medication. The ratio of number of capsules to number of capsules prescribed was less than 0.8 or greater than 1.2. Self reporting is useful in cases of non adherence but often unreliable, overestimaing adherence (Haynes et al 2006, VanWijk et al ,2005). Pill counting which has been shown to have moderate correlation with adherence may provide false record of complete or nearly complete dosing history due to pill 'dumping' or

discarding of tablets prior to the consultation appointment, (Urquhart 2002).

Haynes et al, 2006, systematically reviewed objective methods to improve adherence and their effect on clinical outcome. Techniques ranged from: patient education; information, improved communication between doctor and patient, counselling, self management plans, courses on health empowerment, reminders, manual telephone follow up, personal digital assistants (PDA's)for electronic data capture, supervised lay health monitoring, direct observation of treatment taking, involvement of pharmacists, family intervention and education, psychological therapy, medication charts and units of medical dosage,(Haynes et al, 2006).

Utilizing new technology, mobile phone reminders by voice or text message, paging systems and electronic reminders are all being evaluated, (Haynes et al, 2006)

A variety of simple interventions can improve short-term adherence whilst improving adherence for chronic conditions is more complex, consuming time, effort and resources, often requiring a combined range of interventions,(Haynes et al, 2006).Even the most effective intervention did not lead to large improvements in adherence, clinical benefit and treatment outcome. Less than half the interventions tested in RCTs' improved adherence and less than a third improved outcomes. Benefit of interventions did not appear to be sustained beyond six months and it remained unclear which component of the combination were effective (Haynes et 2006). Frequency of interaction with patients was often beneficial, however, some methods of monitoring adherence, instead of providing the intended positive encouragement may potentially lead to invasion of privacy and loss of autonomy, (Haynes et al,2006).

The WHO report, 2003, indicated the simplicity of the dosage regime and side effects were the therapy related factors that had the greatest influence on adherence

and unlike behavioural factors, therapy related factors are amenable to passive intervention. Refinement of drug delivery systems in conjunction with clear instructions include; Calendar-blister packs or Dossett box organisers with refillable 7-day unit of use dispensing can simplify treatment although elderly patients may still report difficulties, (Connor et al,2004).MEMS, medication event monitoring system, an electronic compilation of dosing history is described as one of the most reliable monitoring systems, (VanWijk et al,2005 ,Vrijens et al,2005). This method records the opening of the container to retrieve a tablet yet does not record what happens to the drug, which may still be discarded.

To avoid over estimation of adherence a more direct approach is to measure the level of drug within the blood stream or urine at a particular time point, (Osterberg, 2005). This technique was utilized in a study investigating the efficacy of Venlafaxine in Atypical facial pain, (Forssell et al,2004).

A novel approach suggested for research trials has been the use of a metabolically pharmacologically inert adherence marker, ingested as an integral part of the medication. (Insull,1984). In theory, measurement of body fluids would indicate the dosage of drug taken but no marker has yet been identified or produced.

Participant retention within clinical studies is always problematic and this study was no exception. Generally in clinical trials adherence is assumed to be high because of frequency of follow up, availability of free study treatment and patient selection, (White,2005).When patients are willing to participate and take the first step for inclusion in a study this indicates a positive attitude towards health care services and may result in increased adherence levels at baseline,(Van Wiljk,2005). This may provide an unrealistic perspective of adherence, within the natural treatment setting,

due to the 'Hawthorne effect, meaning subjects aware of the fact they are being observed show higher adherence due to extra attention they receive, (VanWijk et al,2005). Integrating patients' perspective into treatment plans with the agreement that treatment is more helpful than harmful is another practical way to increase initial adherence,(Bissell et al,2004). Yet, despite regular counselling and monitoring provided at follow up appointments, this is not always enough to maintain patient adherence. Interestingly, in this particular RCT the majority of patients were lost at baseline enrolment but once actively engaged in treatment the actual erosion from the study was minimal. 80% of patients who commenced treatment completed the three month treatment phase. There was no significant difference in the overall adherence to therapy between the four groups. However, those receiving the dual treatment, occlusal appliance and medication had significantly less drop-outs during the study and follow-up period compared to single occlusal appliance therapy. Perhaps, this suggests the dual therapy approach to management, addressing both the physical and medical perspective, is preferred by patients or more simply that the increased time and attention given to dual therapy patients may have improved adherence and retention due to an intangible yet increased level of nurturing.

9.4 Withdrawal

Drop out or withdrawal from therapy is clearly the most severe form of non adherence. Suboptimal adherence and drop out is expensive in both time and resources required, increasing sample size to maintain study power,(Haynes et al, 2006). The systematic review, indicates that perhaps the most simple and effective intervention to improve adherence and prevent drop-out was recalling those who

missed appointments. This is particulary important in a clinical trial and highlights the essential task of ensuring pateints who fail to attend appointments are contacted and retained in care.

Discontinuation of treatment appears to be relatively non-specific for disease or treatment but for antidepressants was found to be related to tolerability of treatment, patient education and quality of clinician and patient relationship, (Nemeroff,2003).

A Cochrane systematic review investigated drop out rates for different antidepressant drugs in order to understand their relative tolerability,(Barbui et al, 2000). Studies using SSRI's showed less participant dropout than tricyclic or heterocyclics but the advantage was only modest (OR 1.21(1.12-1.30). It was considered the antimuscarinic side effects of the tricyclics, not inefficacy, may account for the relatively poor tolerability and suggested earlier RCTs' may have over estimated the difference in drop out between SSRI and TCA, (Barbui et al, 2000). Controlled release antidepressants have the potential to reduce drop-out in the early phase due to lower peak-plasma drug concentrations compared to immediate release formulations and hence more favourable side effect profile. Examples include Venlafaxine XR (extended release) and Paroxetine CR (controlled release) which demonstrate a reduction in some adverse effects.(Nemeroff, 2003).

To enhance participant adherence, increase drop-out and reduce the burden on patient time an internet-based design for clinical studies has been suggested as an alternative approach,(McAlindon et al,2003). It was proposed that this would allow frequent participant contact with less effort for the reporting of treatment outcome measures by completion of on-line computer questionnaires with out the need for lengthy visits to the hospital. However, one limitation is that not all patients may yet have access to the internet hence providing a non representative group of the

population, (Formica et al,2004). In addition patients in some studies, including this RCT, still need to be examined at intervals and one looses the personal contact with the clinician which is known to encourage and maintain treatment adherence.

9.4.1 Withdrawal from this study

Overall adherence levels to medication and withdrawal from treatment was comparable to other RCT's.

Moja et al,2006, in a systematic review analysing trials of SSRI in six trials of chronic daily headache, totalling 301 patients, found there was a 17.3% (27/156) withdrawal from SSRI compared to 15.9% (23/145) from placebo, with no significant difference between the two treatments OR 1.32(CI 0.66-2.64), (Adly,1992, Bendetsen,1996, Landy,1999, Steiner,1998, C d,Amato,1999a, Polisaca, 1992).

In migraine combining four trials, totalling 161 patients, there was a 29.1% (25/86) withdrawal form SSRI compared to 26.7% (20/75) on placebo a non-significant difference between the two treatments, OR1.49 (CI 0.7-3.6),(Adly,1992, C d'Amato, 1999a, Landy 1999, Steiner,1998). This compares very favourably to this study in TMD, where there was a 22% (11/49) withdrawal from SSRI compared to 26% (11/53) withdrawal from placebo, OR1.07 (CI 0.5-2.28), again a clearly non-significant difference

Overall drop out of 18% (36/201) since commencement of treatment compares with 15% (Bendteson, 1996). However, even considering the 49 cases which withdrew before commencing therapy in addition to the 36 during therapy 34% (49+36/250), still compares favourably to the reported drop out of 44% (Adly,1992), 41% (Landy,1999), 38% (Steiner,1998).

In further TMD studies it would be interesting to compare the tolerability of the number of patients withdrawing from treatment between an SSRI, TCA and placebo.

9.4.2 Reasons for withdrawal

The most commonly reported reasons for withdrawal from therapy and follow-up varied between groups. Amongst the medication and placebo groups the most frequently reported reason was 'resolution of pain', 8/63 (12.7%) and 6/63 (9.5%) respectively. In group 3, 10/62 (16.1%) did not return for therapy after the fitting of the appliance which was a significant cause of overall drop-out, $p<0.001$.

'Resolution of pain' as a reason for the medical groups to withdraw from therapy may have seemed the most favourable response for patients to give. Ideally, this would indicate that medication had had an immediate therapeutic response. However, perhaps a more plausible explanation is that patients considered a positive outcome was the expected response and this would avoid offending the clinician and avoid the necessity for further medical therapy and follow up.

In considering why the occlusal appliance group did not return for follow-up may have been for a number of reasons. From an optimistic perspective, wearing the appliance may have resolved the pain and hence the patient saw no reason to return for further management. Conversely, the appliance may have had no effect or increased pain so the patient did not wish to continue with further treatment. In a similar vain, the patient may have found the appliance uncomfortable, not worn, misplaced or lost the appliance, embarrassed to admit to the clinical staff that treatment had therefore not been successful.

Unfortunately, a minority of patients may have seen the study as an opportunity to acquire an upper hard occlusal appliance free of charge. These items are an

expensive commodity when constructed in outside dental practice. However, this scenario would suggest the patient felt no loyalty to the study to return for further treatment but merely considered the appliance as a service provided by the NHS. If this were the case, then one must consider how one could have improved the patient's sense of commitment to the study. At the initial appointment, time and care was taken to build an empathic bond between clinician and patient but this was perhaps not necessarily enough to retain patients within the study. Occlusal appliances were constructed by a second clinician and perhaps there was therefore a unforeseen lack of continuity in the clinical care pathway for the splint only group. The time and effort expected of patients in a study should never be underestimated. As discussed earlier in Chapter 6, time taken off work may involve: lost earnings, lost productivity and even give rise to tension or antagonism amongst co workers and managers. Travel difficulties might involve; expense and distance, tiredness and distress caused by transport delays, strikes or closures which frequently occurred during the course of the trial. Re-numeration for their valuable time and travel expense re-imbursement were not provided for these patients. This lack of financial acknowledgment was perhaps reflected in the rate of erosion from the study and should be taken into consideration when planning a future study.

In consideration of the patient, the timing of appointments were tailored when possible to suit the individual participants, within the constraints of clinic hours. Patients frequently preferred early morning appointments before starting work so clinic times were rearranged to accommodate these early starting times.

The length of appointments, were not dissimilar to standard consultation and follow-up appointments, apart from the necessity to complete several questionnaires in the waiting room at three monthly intervals. Questionnaires almost inevitably became

tedious and repetitive to the majority of patients during the course of follow-up but the need for completion was explained.

Hypothesis (8): There was no significant difference in adverse events between active and placebo medication.

9.5 Adverse events

There is currently no standard technique for identifying adverse events in clinical trials, (Bent et al,2006).Information provided to the patient prior to study participation of the possibility of experiencing side effects is known to influence reporting of adverse events even amongst a placebo group, (Hampton,2006).
In addition the varied methods of compiling information for example open or closed ended questions, short or long check-lists can lead to marked differences in the frequency of reported adverse events (Bent et al, 2006). In this particular RCT, a combination of techniques were employed, with direct questioning related to a short checklist and an open-ended question. The latter would tend to decrease reporting whilst the checklist tends to prompt memory and encourage reporting. Splawinski et al 2006, suggest that to increase the sensitivity for detection of drug-induced adverse effects statistics for efficacy and toxicity should be less stringent and trials should be based on superiority to an active control since placebo adverse effects tend to be disease and treatment specific biased by the nature of the clinical experiment. These criteria were partly followed in this RCT since there was both an active control, the occlusal splint and a placebo drug but an active drug comparator such as a TCA was not included and should be considered for future studies.

9.5.2 Adverse events relating to withdrawal of medication

In relation to the number of patients withdrawing from treatment due to adverse effects of medical therapy, this again compared closely to studies analysing migraine and chronic daily headache. Moja et al,2005, in a systematic review of four migraine trials found a rate of withdrawal due to adverse effects from SSRI to be 7% (6/86) compared to placebo 6.7% (5/75) with no significant difference between the two treatments, OR=1.25 (CI 0.36-4.35), (Adly,1992, d'Amato,1999a, Landy 1999, Steiner,1998). For six studies examining chronic daily headache, withdrawal due to adverse effects were found to be SSRI 3.8% (6/156) and placebo 4.1% (6/145) again no significant difference between groups OR1.02 (CI 0.31-3.34) (Adly,1992, Bendtsen,1996, Landy,1999, Steiner,1998, C d'Amato, 1999a, Polisca,1992). This compares favourably to this study of TMD, SSRI 4% (2/49) and placebo 3.8% (2/53) with no significant difference between groups OR1.08 (CI 0.16-7.37)

9.5.3 Minor adverse events related to mediation

Overall, the minor adverse effects of medical therapy were again similar to those observed in the studies of SSRI in migraine and chronic daily headache. A short meta analysis summarising and comparing the adverse events recorded in these studies is summarised on the next page and reveals some marked similarities. For each condition analysed, there was no significant difference between adverse effects experienced in the placebo and SSRI groups.

The most frequently reported adverse event was insomnia. The increased likelihood of nausea amongst the SSRI group 5/49 (10.2%), reported in this RCT , was not the most commonly reported in the three following studies. However, it was also found to be the commonest adverse event reported in the fluoxetine group, 3/12 (25%), in

an RCT comparing an active comparator with fluoxetine in tension type headache, (Walker,1998).

Table 86: Minor adverse events of SSRI's versus placebo

Study	Condition	N	SSRI	Placebo	OR (95%CI)
Adly,1992 C d'Amato, 1999a	Migraine	84	11/48 (22.9%)	6/36 (16.6%)	1.46 (0.47-4.52)
Adly,1992 Bendtsen,1996	Chronic daily headache	112	17/56 (30.4%)	18/56 (32.1%)	0.92 (0.40-2.09)
This TMD study Leeson, 2006	TMD	201	15/49 (30.6%)	8/53 (15%)	1.79 (0.82-3.91)

Study	Most frequently reported side effects (SSRI)	Most frequently reported side effects (placebo)
Adly,1992	Insomnia & anxiety Strange skin sensations Excitement & insomnia	Insomnia & anxiety Weakness Problems sleeping
C d'Amato, 1999a	Pyrosis Aesthenia Insomnia & excitement	Aesthenia Sleepiness
This TMD study Leeson, 2006	Nausea, Insomnia Drowsiness. Malaise, fatigue, flu-like symptoms)	Headache, rash, GIT symptoms, Malaise, fatigue, flu-like symptoms.

Hypothesis (9) The improvement in pain measures at the end of the RCT are maintained at six and nine months follow-up.

9.6 Follow-up phase

Maintenance and amelioration in pain severity and intensity during follow-up was observable amongst all four treatment groups,(figure 64).

9.6.1 Self report questionnaires : Multidimensional pain inventory

MPI scores in relation to baseline recordings clearly reveal a significant improvement in the patient's overall perspective of pain, notably pain severity ($p<0.001$) amongst all individual groups. Severity, interference, life control and affective distress were significantly reduced ($p<0.001$) when analysing all groups together. However, individually, pain interference significantly improved in groups 1,2 and 3, $p<0.001$, life control, having only improved in group 1 at end of the treatment phase was maintained in follow-up $p=0.007$ with additional improvement in group 3 ($p=0.006$) at the end of follow-up. Affective distress significant in medical therapy groups 1,2 and 4 at the end of treatment was clearly maintained in group 1 at six and nine months follow-up $p<0.001$.Clearly the SSRI medical therapy group appeared to be superior in improvement and maintenance of life control in the marked reduction in affective distress as might be expected from antidepressant medication. In the placebo group life control was not significantly improved either at end of treatment or in follow-up and the improvement in affective distress at the end of treatment was gradually lost during follow-up as would be expected when the placebo effect is lost. No change in affective distress was noted in group 3 (splint only) but life control, not significant at the end of treatment, had improved by the end of follow-up. Life control and affective distress both improved to some extent in group 4 combined therapy. Median scores of all groups during follow-up were generally zero, suggesting maintenance of improvement. Despite the above findings there was no statistical significance between groups amongst outcome measures. Relapse was again not significant between groups with a general 15-20% relapse in scores during follow-up. One would again have expected greatest relapse amongst the group 2 as the placebo effect wore off but observations were not significant

between groups.

Amongst all groups; VAS and PPI significantly improved during follow-up $p<0.001$. Pain response rating was maintained with no significant relapse and there was significant reduction in pain frequency $p=0.029$ and interference $p=0.024$ with no significant difference between groups.

9.6.2 Self report questionnaires : MPQ, BDI and Kellner Illness attitude

The VAS used for the primary outcome analysis was recorded at three and six months post therapy. Interestingly, despite completion of the therapeutic intervention, maintenance and indeed slight improvement in scores were recorded during this time. The linear trend is clearly illustrated in figures 64,65, tables 71,72,73. Although the change could be considered a negligible decrease of a mean 0.5mm, this was nonetheless highly significant $F(2)8.93, p<0.001$ when analysing all groups synchronously.

It appeared to be group 3 , which improved most significantly during follow-up as indicated by intragroup analysis, 1.2mm improvement from 3.19(2.22) to 1.99 (1.78) in the competers analysis and 0.7mm 4.02(2.39) to 3.37 (2.42) using the imputation analysis. One might summise, that patients continued to improve because ,despite instructions to the contrary, they had continued with the occlusal appliance therapy post treatment phase. However, intergroup analysis suggested there was in fact no significant difference in the general level of improvement observed between individual groups. This levelling between groups was again reiterated in the analysis of relapse scores between groups which were once again non significant between groups.

Present pain intensity scores reflects the VAS in exhibiting maintenance and

continued improvement throughout follow up amongst collective groups, $p<0.001$. A report of none or mild pain increased from 154/250 (61.6%) to 168/250 (67.2%) by the end of follow-up. The improvement again appeared to be most profound in group 3 44/62 (71%) to 50/62 (80.6%) $p=0.037$ and group 2, 33/63 (52.4%) to 39/63 (61.9%). However, there was no significance observed between groups. Pain severity showed slight but significant improvement $\chi^2(2)=7.92, p=0.019$, whilst decreased frequency of pain clearly improved by the end of follow-up $\chi^2(2)=14.48$, $p=0.001$.Similarly interference of life due to pain also improved during follow-up $Q(2)=7.42$, $p=0.024$. Group 4 appeared to have a significant decrease in frequency $\chi^2(2)=7.10, p=0.029$ and group 3 the greatest decrease in life interference $Q(2)=7.17$, $p=0.028$. However, such differences did not reach significance between the four study groups. An overall improvement was therefore observed with no discernable distinctions noted.

9.7 Clinical outcome measures

Interincisal mouth opening continued to improve in a similar manner to VAS and the verbal reported scores. Amongst all groups there was a significant improvement in mouth opening $t=(249)6.87, p=0.001$, with a clearly linear trend. (Tables 83,84,85, figures 74,75).However, these results should be viewed with caution since improvement is in the order of magnitude of 0.5-1.5mm and is therefore of no clinical relevance.Although small, improvement measured a mean 0.57mm at FU1 (three months post therapy) and a mean 0.99mm at FU2 (six months post therapy). Improvement appeared most significant amongst group 4 patients with an increase in mouth opening of 1.52mm by end of follow-up $t=(61)\ -2.37$, $p=0.021$. However, as expected inter group analysis found the general level of improvement observed

amongst all groups was not significantly superior in group 4 but revealed a balanced non significance between groups.

A significant element of relapse was noted between the first and second post treatment follow up $p<0.001$, most notable in groups 2 and 3,$p=0.031$. However, this was once again not verified as a significant finding between groups.

The apparent improvement in mouth opening could either indicate a continued improvement in mouth opening over time following cessation of treatment or perhaps simply an observation of the regression towards the mean.

The reason for the apparent, continued improvement in outcome may have arisen for a number of reasons.

Firstly, it may simply reflect a regression towards the mean. Secondly, it may reflect an interaction of underlying factors. During the course of therapy the patient may have become aware of and learned to avoid aggravating factors for the condition. An increased vigilance or avoidance of exacerbating factors would serve to maintain or continue to improve outcome. Alternatively, all patients at the commencement of the study were given informed reassurance and advice on self-management techniques. Continuation of active self-management may again have led to observed maintenance and improvement effect. Finally, one could theorise, that allowing the reparative process to commence over the three month treatment phase may have been the impetus to initiate a more prolonged or ongoing bio psychosocial therapeutic response long term.

X CONCLUSION

10.0 CONCLUSION

10.1 STATEMENT OF PRINCIPAL FINDINGS – Summary of results

10.1.1 Primary outcome measure

Overall, the results of the study are positive with all four treatment groups ;SSRI, bite guard, SSRI with bite guard, and placebo; showing a significant reduction in the primary outcome measure of pain severity (VAS) over the three month treatment period, $p<0.0001$.The positive response to treatment may occur as a result of the active treatment, a regression towards the mean, the natural history of the disease, the therapeutic environment and the strength of the doctor-patient relationship. There was no significant difference in efficacy observed between the therapeutic groups under investigation; SSRI, bite guard, SSRI with bite guard. Therefore, this suggests that an SSRI (fluoxetine: Prozac) in combination with a bite guard is equally effective to an SSRI or bite guard alone in the treatment of chronic TMD. **[Hypothesis 1a]**

In comparison to placebo, there was no difference in efficacy between bite guard and placebo or combined therapy and placebo. However, there was evidence of a significant improvement in >50% pain reduction on the VAS amongst the SSRI group compared to placebo, with an effect size of 2.07 (CI 1.16-3.70). This suggests that an SSRI (fluoxetine;Prozac) in daily oral doses of 20-40mg is more effective than placebo in the treatment of patients with chronic TMD. **[Hypothesis 1b]**

10.1.1.1 >25% pain improvement at three months

Not surprisingly, all four groups achieved the more attainable >25% improvement in pain severity on the VAS at three months $p<0.0001$. However, the significant difference in efficacy found between fluoxetine and placebo at >50% improvement,

was no longer observed. This suggests the SSRI may achieve a greater reduction in pain in more patients than placebo.

10.1.1.2 NNT analysis

The NNT for >50% pain relief (ITT analysis, N=201) were: fluoxetine:4.1 (CI 2.5-17.2) stabilization appliance:14.8 (CI 4.3-∞), combined therapy, fluoxetine and stabilization appliance;7.8 (3.40-20.7)and for >25% pain relief: fluoxetine:5.6 (CI 2.80-76.80), stabilization appliance:13.1 (CI 3.80-∞), combined therapy, fluoxetine and stabilization appliance;5.8 (2.90-46.1).The NNT of 4.1 or 5.6 for fluoxetine is a similar to previous systematic reviews for SSRI's in pain indicating an NNT of 6.7,(Chung,2005).

10.1.2 Patient study characteristics

Patients were predominantly female 76% (191/250); employed 67% (167/250), in the third decade of life, mean age 32(SD 9.6) (range 16-55).These findings were comparable to previously reported TMJ clinic populations, (Helkimo, 1974, VonKorff et al, 1988, Dworkin et al, 1990, List et al, 1999, Truelove et al, 2006). Demographic and epidemiological features of the study cohort were consistent with the patient population seen within secondary or tertiary TMJ clinics. **[Hypothesis 2]** TMD pain was typically described as a unilateral 72% (180/250), constant 74% (185/250), dull ache 64% (161/250), discomfort 54% (137/250), with occasional sharp episodes 40% (99/250), of approximately three years duration, mean 3.3 (SD4.5) years (range (3 months-32 years). 26% (66/250) reported dental treatment to be a precipitating factor whilst frequently reported provoking factors included: chewing 77% (192/250), yawning 76% (191/250), biting 66% (164/250) and emotional tension 54% (134/250).

Sleep disorders related to pain, included prevention of sleep 45% (113/250) and disturbance of sleep 46% (117/250). Co-morbid recurrent chronic pains included; headache 61% (153/250), neck ache 50% (125/250), backache 48% (121/250), migraine 32% (82/250) and abdominal pain 30% (74/250).

Duration, location and character of TMD pain are similar to those patients presenting to other secondary and tertiary TMJ clinics, **[Hypothesis 3].** (Ohrbach,1995, Dworkin and LeResche,1999, LeResche and Von Korff, 2005, Truelove et al, 2006)

10.1.3 Secondary outcome measures summarised

Secondary outcome measures also showed significant amelioration amongst all groups. This included: self report verbal rating scales of present pain intensity ($p<0.001$), frequency ($p<0.001$) and interference ($p<0.001$).This was also observed in the pain and psychosocial self report pain questionnaires, notably MPI: severity, interference, affective distress and improved life control together with MPQ: VAS, PPI, total, sensory and affective components. Clinical outcome measures revealed significant improvement in interincisal mouth opening, character of TMD pain and other co-morbid chronic pains.

10.1.3.1 Outcome predictors

Logistic regression analysis of outcome predictors suggested a decreased chance of a successful >50% pain improvement at three months, in those with a longer duration of TMJ pain OR=0.84 (0.71-0.99), presence of co-morbid backache at the initial consultation OR=0.36 (0.38-0.94), higher the score rating of: Kellner,disease phobia OR=0.64(0.38-0.94); MPI punishing response of significant family and friends OR=0.63 (0.41-0.99) and increased social activities OR=0.37 (0.18-0.76) at initial

presentation. Positive predictors of outcome included initially high scores in MPI general activity level OR=3.42 (1.09-10.13), clinical VAS OR1.4(1.12-1.77) and abdominal pain OR=3.66(1.22-11.0).

For >25% improvement in pain at three months, only initially reported MPI; support of significant family or friends OR=1.26 (1.00-1.59) and outdoor activities OR=1.40 (1.01-1.94) were significant positive predictors of outcome.

10.1.4 Pain severity and influence on life.

A significant improvement in PPI (intensity) ($p<0.001$), interference ($p<0.001$) and frequency ($p<0.001$) of TMD pain was recorded by the clinician for all groups. **[Hypothesis 4a].**This was consistent at all time points of the study; four, eight and twelve weeks with no significant difference between groups.

A significant improvement in 'self-recorded' patients perspective of pain was recorded for all groups, MPI severity ($p<0.001$), interference ($p<0.001$) and affective distress ($p<0.001$) with an increased level of control in life ($p<0.001$). Inter group analysis revealed no significant difference between groups. MPQ total, sensory and affective components, VAS and PPI all showed significant improvement ($p<0.001$) with no significant difference between groups. **[Hypothesis 4b]**

10.1.5 Depression

A significant improvement in depression was recorded, using the BDI, on completion of the study, $p<0.005$, with no significant difference between groups.

[Hypothesis 4c]

There was a reduction from a median score of 7.00 (25^{th} and 75^{th} percentiles 3.00-13.00) at the start of therapy to 5.00 (2.00-12.00) on completion of therapy. This indicates the majority of patients were clinically non-depressed throughout

treatment. However, there was a broad variation in scores with come patients classified as suffering from severe depression at baseline. This was investigated further in the post hoc sub-group analysis.

10.1.6 Illness attitude and behaviour

A significant reduction in Kellner, hypochondriacal beliefs and illness attitude was observed for all groups, $p<0.05$, with no significant difference between groups.**[Hypothesis 4d]** Although the SSRI group appeared to have the most significant reduction in hypochondriacal beliefs this was not significant in inter group analysis.Kellner, disease phobia was not significantly reduced in any group.

10.1.7 TMD signs and symptoms

A significant improvement in the signs and symptoms of TMD were recorded in all groups on completion of the study. **[Hypothesis 5a, 5b]**

There was a significant reduction amongst all groups in TMJ pain, $p<0.001$ and muscle discomfort, $p<0.05$. A reduction in TMJ pain was not apparent in the SSRI group, $p=0.08$ but this did not reach significance in intergroup analysis. Temporalis muscle pain only decreased significantly in the splint only group $p<0.005$ but again this did not reach significance between groups. The combined splint and medical therapy group however showed the most significant reduction in reported masseter muscle discomfort which was significant between groups, $p=0.008$ and may indicate a synergistic therapeutic response.

The dull and sharp pains of TMD had both significantly reduced, $p<0.001$, by three months. However, in intergroup analysis the dull ache had reduced most significantly in SSRI ($p<0.001$), combined therapy ($p<0.005$), placebo ($p<0.05$) but not in splint only ($p=0.38$) which was a significant difference between groups

(p=0.008). In addition there appeared to be an increase in reported facial, ear and tooth pain in the splint only groups which was significant between groups, (p=0.002, p=0.003, p=0.009 respectively).This unusual finding may be related to an increased awareness of the face, preauricular region and teeth in those wearing an occlusal appliance.

Interincisal mouth opening significantly improved with a clearly linear trend and no significant difference between the four observed groups.

10.1.8 Co-morbid pain conditions

A significant improvement in co-morbid pain conditions were recorded on completion of the study including; headache, migraine, neck ache, backache and abdominal pain, $p<0.001$, with no significant difference between groups.

[Hypothesis 5c, 5d]

10.1.9 Subgroup analysis summarised

Although not significant in inter group analysis, individual groups show a trend towards a more significant improvement with medication in depressed categories and a more significant improvement in non-depressed categories in the placebo and splint alone groups. Results from the study therefore might tentatively suggest depression has an influence on several aspects of TMD. **[Hypothesis 6a]**

Unexpectedly, depression was unrelated to the duration of pain but was related to a slightly older age group. The depressed group had a significantly higher proportion of concomitant pain conditions at baseline which did not decrease as significantly as the non-depressed, post treatment. They also had a higher incidence of self-reported prevention and disturbance of sleep $p<0.01$ and higher emotional initiating $p<0.05$ and provoking factors $p<0.001$ for TMD. However, other co-variates may have

influenced this finding; psychosocial measures suggested increased hypochondriacal beliefs and disease phobia, whilst MPI suggested decreased life control and decreased activities away from home, together with an increased punishing response from significant family and friends amongst the depressed group.
Clearly, as in all pain conditions, depression has an interesting relationship to TMD which, together with sleep, psychosocial factors and particularly co-morbid pain conditions requires closer investigation.

There was no significant difference in pain improvement between those patients with high or low initial pain scores. **[Hypothesis 6b]** However, for those with initially high MPI pain scores, there was a trend for a greater reduction in pain in those with a high initial MPI pain score compared to those with a low initial MPI pain score. However, this was not confirmed by inter-group analysis. BDI improved significantly in low initial pain scorers but not high initial pain scorers. Illness attitude only improved in high pain scorers whilst headaches only significantly decreased in those with low initial pain scores $p<0.008$.

Clinical and pain history characteristics at baseline did not separate treatment responders from the non-responders. **[Hypothesis 6c]** However, demographic and psychosocial factors were indicative of response. A higher percentage of no responders were referred from the tertiary care sector suggesting more complex or recalcitrant TMD cases unrelated to the duration of pain. Interestingly, a higher percentage of divorcees were noted to be non responders the reason for this was unclear. Similar to the depressed category, an uncaring attitude or punishing response, from family and friends was higher amongst non-responders ($p<0.036$). However, dissimilar to depression, increased frequency of participation in social

activities was higher in non-responders ($p<0.036$). These descriptive trends would certainly suggest the need for closer investigation of subgroup covariates.

10.1.10 Adherence summarised

There was a significant difference between adherence to splint wear in the occlusal appliance only group compared to the combined occlusal appliance and medication group, χ^2 (1) 4.78 p=0.029. **[Hypothesis 7]** However, there was no significant difference between adherence to medication in the SSRI, placebo and combined therapy groups. The time scale of withdrawal from treatment was not significant between groups. Within groups the predominant reason for withdrawal was; not wanting to receive splint therapy (p=0.006) or acquiring a splint and not returning to the study ($p<0.001$)

10.1.11 Adverse events summarised

There was a significant difference between SSRI and placebo medication in adverse events reported following the initial treatment phase at four weeks. This occurred in both SSRI alone OR= 2.8(1.0-7.7) and SSRI with occlusal appliance OR=2.7 (1.0-7.5). However, there was no significant difference in adverse events reported during the subsequent eight and twelve weeks of therapy. **[Hypothesis 8]** The most frequent reported adverse event was nausea in the SSRI group 5/48 (10.2%) and combined therapy group 8/48 (16.7%). Walker, 1998, reported a similar finding of nausea in a TTH study of SSRI 3/12 (25%).

10.1.12 Follow-up post RCT

Improvement occurred not only during the course of the three month treatment period but was maintained throughout the six and nine month follow up phase. **[Hypothesis 9]**

Despite the discontinuation of treatment at the end of the three months, maintenance and amelioration in TMD pain related scores was observed amongst all four groups. All groups showed a continued improvement in interincisal mouth opening $p<0.001$ and VAS $p<0.001$ during the follow-up phase. Similarly, PPI $p<0.001$, frequency $p=0.001$ and interference $p=0.024$ significantly improved during follow-up. Significant improvement was observed in MPI severity $p<0.001$, interference $p<0.001$, affective distress $p<0.001$ and increased level of life control $p<0.00$ when all groups were analysed together. Within the individual groups affective distress was only significantly maintained in the SSRI group during follow-up $p<0.001$. Life control only significantly improved in the SSRI group $p=0.007$ at the end of treatment phase and this effect was maintained during follow-up, whilst in the splint group although there was no difference after treatment a significant improvement seemed to appear, $p=0.006$, during follow-up. These observations were however not significant between groups.

10.2 VALIDITY OF STUDY RESULTS – STRENGTHS AND WEAKNESSES

The quality of a trial and the elimination of bias relies on clear reporting of design, clinical conduct and coherent analysis, (Jüni et al, 2001, Altman et al, 2001). Internal validity is required for external validity and relates to minimizing systematic error or bias in: selection, performance, attrition and detection, between groups of patients within clinical trials, (Jüni et al, 2001).

10.2.1 Internal validity

10.2.1.1 Selection bias

Firstly, avoidance of selection bias relates to generation and concealment of randomised allocation to comparative groups (Altman and Bland,1999). This was

achieved in this study by computer generated block randomisation sequence and concealment from study personnel, as explained in Methods, Chapter IV.
Stratification of randomisation can be considered when evidence suggests that particular characteristics are predictive of outcome, (Therneau, 1993, Kernan et al, 1999). However, TMD is multifactorial, making it complex to categorise specific features. Knatterand, 2002, suggest that with more than 40 study participants, there is a good probability of achieving balance without stratification. With the numbers allocated per group in this study and the evidence that there were no significant differences between the baseline variables, as indicated in Chapter VI, it can be assumed that there was a good probability of balance between the four groups without additional stratification. Avoidance of selection bias is therefore a strength of the study.

10.2.1.2 Performance bias

To prevent performance bias the subjects receive equivalent care apart from the treatment under investigation (Jüni et al, 2001). In this study, no additional care was knowingly given preferentially to one of the four treatment groups. However, those receiving combined therapy were naturally and unavoidably exposed to increased clinical time and attention, which could be considered a study weakness. Nevertheless, this did not appear to improve outcome.

10.2.1.3 Attrition bias

To avoid attrition bias, care is taken in dealing with protocol deviations and loss to follow-up, (Jüni et al, and 2001). To avoid bias, ITT and imputation analysis were reported, rather than only completer's analysis, as previously discussed, in Chapter

VI. Protocol deviations were reported to explain attrition, in Chapter IX. Avoidance of attrition bias could therefore be considered strength of this study.

10.2.1.4 Detection bias

This only occurs if those recording outcome are influenced by the knowledge of patient allocation, which is avoided by blinding the assessor and maintaining concealment, (Noseworthy et al, 1994). Concealment or double blinding was maintained with regards to drug and placebo. This was achieved by administrative and nursing personnel being responsible for the allocation and concealment of drug identity from the clinician. The latter dispensed the bottle of tablets to the patient but was unaware whether the bottle contained drug or placebo.

However, it was not possible to remain blind with regards to which patients were receiving splint or combination treatment, since the clinician providing treatment and assessing outcome and adverse effects were one in the same person. This may be considered a slight weakness of the study.

10.2.1.5. Multiplicity and multiple outcomes (Type 1 errors)

Multiplicity refers to the plethora of possible data comparisons in a RCT (Altman et al, 2001). Multiple comparisons or analysis of the same data reduce statistical power and increase the risk of false positive or type one errors, when a difference attributed to the intervention is more probably due to chance, (Altman et al, 2001). Sources of multiplicity may arise from numerous factors including: the use of multiple outcome measures, multiple intervention groups, repeated measures over time and subgroup analysis, (Peduzzi et al, 2002, Pocock et al, 2002).All varieties of multiple outcomes have obviously been utilized in this study, which potentially could have been considered a study weakness. However, as in most clinical trials, multiple outcomes

are required. An individuals response to treatment is multifaceted and clearly within a RCT analysing a range of aspects is important, (Peduzzi, 2002). Secondary outcomes such as improvement in interinscisal mouth opening or improvement in other concomitant chronic pains, introduces extra variability. Nevertheless, secondary analyses are important to our understanding of the condition even though it is a less direct measure of effect, (Moja et al, 2005).

Analysing data at different time points and using a range of rating scales increases the number of comparisons. This is clearly observed in the analysis of this RCT, where data was analysed not only at treatment completion but at monthly intervals throughout treatment and three month intervals post treatment follow-up. Additionally a vast range of rating scales were employed. The mass of findings produced can result in misleading findings of significance occurring by chance (Altman et al, 2001)

Prespecified and prioritised outcome measures are therefore required to avoid some of the inherent problems of multiplicity from post hoc data interpretation (Proschan and Waclauriw, 2000, Peduzzi et al, 2002). The trial should be powered and monitored on the basis of a single primary outcome variable with all other outcomes defined as secondary or tertiary, (Peduzzi et al,2002). This advice was followed in this RCT where there was a clear primary outcome measure of >50% pain improvement on the VAS and all other outcomes classified as secondary, hence reducing the risk of type one errors and increasing the studies strength.

10.2.1.6 Treatment sample size (Type 2 errors)

Small sample sizes, with insufficient power to detect important differences between drug and placebo, may lead to false negative, type two errors, (Altman et al, 2001). Kjaergaard et al, 2001, suggest trials of less than 30 subjects per group artificially

inflate estimates of treatment effect. In a systematic review of SSRI in migraine and TTH the median sample size for randomised groups was 50 (interquartile range 39-55). However, the mean drop-out rate was 20%, ranging from 20% to greater than 40%, so the effective sample size was in fact smaller,(Moja et al,2005).

The number of individuals exposed to a drug should obviously be kept to a minimum, since although potentially beneficial the drug may also be in-active or indeed harmful. Studies using active comparators tend to require larger numbers of patients than placebo controlled trials possibly exposing more patients to potential harm, (Emanuel and Miller, 2001). Empirical evidence suggests placebo controls reduce the number of symptomatic individuals in a RCT producing an inverse relationship between sample size and detectable population effect size, (Linde et al, 2003, Leon, 2001). However RCT, whether large or small, if adherent to strict criteria yield high quality results close to the average for treatment studies, (Juni et al, 2001).

In this placebo controlled TMD study the initial numbers per group were 62 or 63 and at the end of three months treatment were 38 to 43. Sample size could perhaps have been even larger to detect more significant differences. The majority of patients withdrew at baseline. This may have been avoided by ensuring patients with minimal pain at baseline were not included in the study and further efforts made to decrease attrition from the study at baseline outset, to increase power and design sensitivity.

10.2.2 External validity – strengths and weaknesses in relation to other studies

External validity, otherwise termed 'generalisability' relates to the 'applicability' of results to other situations or clinical settings and is dependant on the provision of adequate study information (Altman et al, 2001).

Care was taken throughout study reporting to provide as much relevant information with regards to the study cohort as possible. The demographic and epidemiological features of the study cohort were comparable to the worldwide TMD clinic population, suggesting results could be extrapolated to a broader clinical setting, as discussed in Chapter VI. Future research studies should however utilise the RDCTMD criteria for patient assessment, which are now used internationally and have been validated for TMD research, (Dworkin and LeResche, 2001).In defence of the approach undertaken in this study, the assessment did fulfil the criteria at the time of study design of a dual axis approach examining both the clinical history and examination together with psychosocial measures. Use of the RDCTMD in the future, would however allow direct comparison of subgroups with other worldwide cohorts of TMD patients.

10.2.2.1 Study design structure– in relation to other studies

This was a four armed (factored), prospective, parallel design, double blind for medical therapy, RCT. A cross over design, utilising the same subjects twice, has the advantage of eliminating the between patient factors which can cause considerable variation in pain perception and reporting,(Louis et al,1984, Jones Kenward,1989, Ratkowsy 1993,Senn,1993) This decrease in variance and increased statistical power reduces the number of patients required,(Louis et al,1984).This type of design was employed in the well constructed, double blind RCT investigating the efficacy of Velafaxine in AFP, incorporating an interposed two week wash out period, (Forssell et al,2004).

However, cross over design is not generally recommended for antidepressant medication, within the field of depression, since the favourable response may persist for months after discontinuation of the treatment, (Prien, 1994). This 'carry over

effect' may result from the prolonged action of medication or metabolites, change in the central or peripheral nervous system, behavioural or psychological response over time and hence altered response to subsequent treatment, (Moja et al, 2006). Such factors may also relate to the treatment of TMD pain and parallel group design as utilized in this RCT hence avoids concerns related to the 'carry-over effect' and is hence a strength of the study design.

10.2.2.2 Adherence measures – in relation to other studies

No venous blood samples were collected at treatment visits to determine serum levels of fluoxetine and its metabolite norfluoxetine, as was undertaken in the study of Venlafaxine in AFP (Forsell et al 2004). Although a useful measure of adherence, this may also have disadvantages since patients generally dislike extra blood tests which additionally would have increased laboratory expenses.

Alternatively, MEMs may be used or diary record cards to indicate medication adherence as discussed in chapter IX.

10.2.2.3 Adverse effects – in relation to other studies

The same investigator assessed adverse events and efficacy outcomes. However, this discrepancy was also noted amongst other SSRI trials in TTH and migraine, (Moja et al, 2005).In future studies extra personnel would need to be employed to assess adverse events and efficacy outcomes separately to avoid any potential bias.

10.3 RESULTS IN THE CONTEXT OF RELATED RESEARCH

This study has not clearly indicated a significantly measurable difference in efficacy between medical and physical therapies either alone or in combination.

Failure to demonstrate a difference between two treatments is not necessarily proof of equivalent effect for the intervention under investigation, (Hotopof et al, 1997, Jones et al, 1996). Regardless of outcome, the results of a RCT have an important application in clinical research when interpreted in the context of earlier studies, related research and existing evidence, (Clark et al, 1998).

10.3.1 Medical therapy in TMD

Although there are no previous studies published comparing SSRI medical therapy with splints there have been other studies assessing the efficacy and tolerability of SSRI's in the treatment of tension type headache (TTH) and migraine, analysed in a systematic review,(Moja et al, 2005). This is particularly pertinent, since long-term studies suggest TTH to be closely related to TMD, (Egermark et al, 2001, Magnusson et al, 2005,). The similarities are currently being investigated, (Orbach,2006).
Four studies compared fluoxetine versus placebo, (Adly et al,1992, C d'Amato et al,1999, Polisca et al, 1992 and Steiner et al,1998).Three studies compared fluoxetine versus amitriptyline, (Oguzhanoglu et al,1999,Walker et al,1998, Krymchantdowski et al , 2002,).Reassuringly, similar to the response observed in this current RCT, Moja et al, 2005, found SSRI's only to have similar efficacy to placebo in the treatment of migraine headache over the two months of treatment.

There is some evidence that SSRI's are well tolerated with respect to minor adverse events but this did not have an impact on total number of dropouts in this RCT of TMD or earlier studies, (Moja et al, 2005). Bank, 1994 and Langermark and Olessen, 1993 in studies of SSRI in migraine and tension type headache reported a 20% or more loss to follow-up. Greater than 30% loss was reported (Steiner, 1998, Walker et al 1998 and Krymchantowski, 2002); whilst greater than 40% was

recorded by (Adly 1992, Landy, 1999.) This relates favourably to the 18% reported in this TMD study.

It has been shown that during the first part of treatment patients are more tolerant of adverse events because of the perceived benefit of taking medication whilst three months ensures that the patient gains sufficient clinical benefit, (Moja et al, 2005). The issue of long-term treatment of greater than three months could be investigated further in TMD. However, the recommendation that antidepressants are prescribed for six months is based on evidence measuring their pharmacological effect in depressed patients and not for the treatment of chronic pain, (Paykel and Priest, 1992, Montogomery et al, 1988, Guaiana et al, 2004).

In addition, length of follow up could be extended. Moja et al, 2005, recommends a twenty four week length of follow up suggesting twelve weeks is too short to achieve an effect. Further follow up of this particular cohort of TMD patients could be undertaken, particularly in relation to relapse and the use of concomitant analgesics. The relative probability of relapse can only be investigated by lengthening the period of follow-up to 5years, ten years or perhaps beyond.

Other trials have used TCA instead of SSRI. When compared to TCA, SSRI's were less efficacious in the treatment of TTH. TCA significantly reduced headache duration by 1.26 hours/day and marginally reduced headache indices but the reported adverse events were greater. It was reported that results were based on short term trials so results may not generalise to longer term treatment beyond three months. However, this is an interesting finding since previous studies using the TCA, amitryptyline and dothiepin in mixed chronic facial pain both showed a favourable reduction in pain (Feinmann and Harris, 1984, Sharav et al, 1987). Although, in a more recent study of facial pain, Amitryptyline was found to have no

significant reduction in pain severity but significant reduction in the perception of stress, (Raigrodski et al, 2001).

The differences in selectivity of SSRI and TCA could be related to differences in efficacy but the mechanisms of efficacy in TMD, orofacial and headache prevention and pain relief remain unclear, (Ansari,2000). Research is required to establish and more fully understand drug dosage response in orofacial and TMD pain particularly in relation to the length of maintenance and relapse prevention.

Amitryptyline or an alternative TCA, with less antimuscarinic side effects, could certainly be considered as an active comparator in terms of clinical efficacy in future TMD studies. This suggestion was also put forward for patients with chronic TTH (Moja et al, 2005).

The effect of SSRI's in pain is not due to a direct antidepressant effect, (Sindrup and Jensen, 2000). Moja et al, 2005, suggests avoidance of the confounding effects of antidepressant treatment could be achieved by comparison of the SSRI with a non-antidepressant prophylactic drug or non-pharmacologic preventive treatment. This was in fact the approach undertaken in this research study comparing SSRI with a bite guard and combined therapy. An RCT which evaluated the efficacy of an SSRI versus CBT, in a group of mixed chronic facial pain and TMD, showed pain reduction at three months with fluoxetine compared to placebo which was maintained on cessation of drug therapy, (Harrison et al, 1997).However, a further RCT evaluating an SNRI, venlafaxine, did not find a significant reduction in pain severity but moderate pain relief with decreased need for analgesic consumption amongst the active group. Unfortunately, this current TMD study did not quantify or document additional analgesic use during the three month course of treatment.

No studies were identified comparing SSRI with a drug other than an antidepressant or with a non-pharmacological physical treatment as utilized in this study of physical splint therapy versus SSRI medical therapy.

10.3.2 Occlusal appliance therapy in TMD

Numerous studies have investigated the use of bite guards in the treatment of TMD. Since commencement of this RCT, several systematic reviews and met-analyses have been published in the field concluding that there is insufficient evidence to support the role of occlusal appliances in TMD, (Raphael and Marbach, 1997, Dao et al, 1998). Dao et al, 1998 suggested until more is known of the aetiology and natural history of TMD, splints were useful adjunctive therapy. Forsell et al, 1999, in an extensive systematic review concluded that although evidence for occlusal adjustment was lacking, splints showed some benefit in TMD. Kriener et al, 2001, assessing 10 occlusal studies, optimistically concluded there was sufficient evidence to support splint use in the management of localised myalgia and arthralgia. However, the majority of results do not justify definite conclusions about efficacy of splint therapy, (Raphael, 2001, Ekberg and Nilner, 2002, Turp et al, 2004, Forssell, 2004). Current opinion suggests there is weak evidence that stabilization appliances are more effective than other splints in reducing muscle and joint pain, (Ekberg et al,2003, Magnusson et al, 2004, Wilkinson,2005). Al-Ani et al, 2006, however, in a Cochrane systematic review, did not find significant evidence to confirm whether stabilization splints can reduce pain caused by painful TMD.

This TMD study has also not been able to provide any further conclusive findings. Future research, into splint usage in TMD could incorporate a waiting list control group but more importantly focus on which target subgroups benefit most from splint therapy. In particular, level of bruxism and sleep patterns could be analysed as

covariates. In fact, much research is already being done in relation to TMD, sleep bruxism, splint therapy and antidepressant medical therapy (Lavigne et al, 2005).

10.4 CLINCIAL SIGNIFICANCE – MEANING OF THE STUDY

Clinical significance is defined as a return to normal functioning, (Jacobson et al, 1999). Apart form effect size and NNT, group differences provide limited information on individual response to treatment and clinically meaningful improvement in symptoms, (McQuay and Moore, 1999).

At the end of the three month treatment, a statistically significant overall improvement in the VAS of 2.5cm (5.77cm(SD2.29) to 3.25cm(SD2.41),$p<0.001$) for completers or 1.7cm based on an imputation analysis (5.77cm (SD2.29) to 4.06cm (SD2.57), $p<0.001$), may not lead to a return of normal function for specific individuals. Even with a more direct clinical measure of interincisal mouth opening, a statistically significant improvement ($p<0.001$) of 2.81mm (38.81(SD 9.36) to 41.62(SD9.22) for completers and ($p=0.018$) 1.38mm from 38.90(SD9.35) to 40.28(SD9.52) based on imputation analysis, may not again necessarily imply clinical significance. Reliable change in a patient's condition can be difficult to quantify. To demonstrate 'recovery' the statistical change in the condition must be within 'normal range of function' but a statistical change in a condition such as TMD may still render the patient 'dysfunctional', 'improved but not recovered'. Therefore discrete cut-off points can misclassify individuals into false positive, falsely recovered.

There is diversity in the presentation of TMD even within the normal population. Patients range from the completely healthy, functioning, asymptomatic, to functioning symptomatic, mildly dysfunctional to moderate or severe dysfunctional. For this reason subgroup analysis was performed to try to determine if there were

any significant differences in outcome according to level of depression, level of pain severity at base line and characteristics of those categorised as responders to therapy. Although trends were demonstrated, that could be investigated further, no clear indicators were proven.

Ultimately, clinical significance of treatment relates to the qualitative satisfaction of the patient with therapy, quantitative decrease in pain and increased functional ability. These may vary subjectively for a particular group of patients or between individual patients.

Information on benefit-to-risk ratio for a specific individual is derived from research data using NNT which incorporates baseline readings with therapeutic effect, (Altman, 1997). Transposing the results of research to different clinical settings might be problematic when patient characteristics differ considerably form the typical trial participant. Hotopof et al, 1999 suggested patients with headaches should be studied in real life situations and again this could be extrapolated to the condition of TMD. The potential benefit and harm of an intervention must also be considered in the light of the patients preferences for therapy, (Altman et al, 2005).

10.4.1 The individual TMD patient

Customised clinical treatment and care pathways have always seemed an anathema to the empathetic clinician. Nowadays, there is almost an obsession with developing rigid care pathways, management protocol and guidelines. However, one must never overlook the obvious. Patients are distinct individuals who cannot be compartmentalised into organised categories. This is especially true when dealing with a condition such as TMD where aetiology is currently deemed complex and multifactorial. At present, the clinician must rely on evidence based medicine derived

from systematic reviews of RCTs, together with clinical experience and intuition, to gauge the most appropriate treatment for the individual patient.

Randomisation as a standard design feature of clinical trials is aimed at determining treatment effect for a particular disease or condition within a population sample, (Altman et al, and 2001). Knowing how to apply study findings to individual patients is more complex however since randomisation does not always lead to unbiased estimates of treatment effect when important, yet unrecognised covariates are neglected, (Altman et al,2001, Liu et al,2005). In an attempt to address this issue, Ford and Norrie, 2002, examined the use of covariates in the potential benefit or risk for an individual subject exposed to a particular treatment. Pocock et al, 2002, examined baseline data, subgroup analysis, covariate-adjusted analysis and baseline comparisons; whilst the impact of population heterogeneity on estimated treatment effect was predicted using a set of simulated logistic regression models,(Lui et al, 2005).

Research suggests, treatment beneficial in some subjects may indeed be ineffective or even harmful to others with specific characteristics, and clinical response to treatment and drug metabolism may be influenced by environmental and biological factors,(Liu et al,2005).Environmental factors may include; climate, smoking and alcohol consumption whilst biological factors may include: genetics, age, gender, race and ethnicity.

Individuals may have significant differences in rate of drug metabolism, clinical response to drug and side effects, (Burroughs et al, 2002). 35% of the population do not respond to β blockers and 30% do not respond to statins, (Tanne, 1998). Modern biomedicine and advances in human genomics may distinguish genetic susceptibility to drug treatment, an enhancement or reduction in sensitivity. (Liu et al, 2005).

Genetic polymorphism has been found to influence positive and adverse reactions to

antidepressants and antipsychotics leading to suboptimal treatment in individual patients, (Kirchheiner et al, 2003). With genomics, rather than waiting weeks to determine whether a drug is effective for a particular patient, the most appropriate treatment can be implemented immediately, (Cardon et al, 2000). This may allow choice of drug treatment specific to the patient's genotype, potentially identifying the right drug and dose for each individual, (McCarthy and Hilfiker, 2000)

Predicting drug response could potentially save time, money and even lives.

Racial and ethnic variation also affects response to medication due to difference in metabolism for example; codeine is more effective in East Asians than Caucasians, (Burroughs et al, 2002). In another study, using the SSRI, paroxetine, to treat mood and anxiety disorders, Hispanics and Asians had a lower response rate. However, Asians had the highest full response and Hispanics the lowest. The latter also showed the higher placebo response but adverse effects were similar across groups, (Roy-Byrne et al, 2005).With antipsychotic medication white Caucasians required a higher dose of medication than Asians and Hispanics to achieve similar blood levels, (Burroughs et al, 2002).

Similarly, heterogeneity in the population including genetic polymorphism may influence an individual's response to TCA and SSRI in the treatment of TMD.

Philips et al, 2001, conducted a study to show the clinical implications of gender in acute TMD, concluding that biopsychosocial differences amongst gender would suggest that certain treatments are more beneficial between respective males and females. In recent years, research has also suggested there may be a genetic component to TMD, (Feng et al, 2004).

Individual variation in the characteristics of the condition and coping strategies may also be relevant in TMD. Raigrodski et al, 2001, investigated the effect of amitryptyline on bruxism in a four week cross over study design and found that the

drug did not decrease pain intensity but was useful in the management of the perception of stress levels associated with sleep bruxism.

Molina et al, 2000, analysed the profile of TMD bruxers and TMD non bruxers amongst five year consecutive referrals. The chief complaints of joint noises, facial, TMJ, head and cervical pain were recorded in both groups. However, severity of bruxism behaviour dictated an increased need and utilization of health services including increased consultations, increased occlusal splint usage and increased need for mediation; analgesics, muscle relaxants and antidepressants. The study confirmed that pain is the major complaint of TMD patients with bruxism and reinforces the view that different subgroups of TMD and severity levels of bruxism exist. Differentiation of subgroups by questionnaire assessment of bruxism severity was suggested in order to direct the approach to therapy.

Results from the subgroup analysis of this study might tentatively suggest depression has a role to play in response to therapeutic outcome in TMD.

Rammelsburg, 2003, in longitudinal studies reported muscle disorders, classified using the RDC to be mainly chronic or fluctuating pain conditions with 31% remission. Psychopathology appears to be associated with muscle disorders rather than disc or joint disorders (Kight, Gatchel and Wesley, 1999).

A disturbance in sensory function amongst TMD patients' has also been reported, (Svensson et al, 2005).

Gender, genetic components, altered sensory function, level of bruxism, associated psychopathology and depression are just a few of the examples of the plethora of individual variables and confounding factors in TMD. The age, duration of pain, previous contact with health care services and therapies received, health locus of control, past history and experience of pain, lifestyle and daily commitments, psychological behavioural and coping strategies are but a few of the endless list

which all impact on the individuals ability to respond to the therapy provided at a particular point in time.

10.5 RESEARCH STUDY IMPLICATIONS FOR CLINICIANS AND POLICY HOLDERS

The research study implies that a significant improvement in outcome measures is achievable in TMD patients provided with therapy within a research study, conducted in a specialist centre. The cohort receiving care had suffered from TMD for a mean 3 years yet the condition was amenable to improvement. This improvement was then sustained for up to a year, even after discontinuation of therapy, whilst patients were maintained under review within the research study. What remains unclear is which interventive therapy is the most beneficial. Although all groups improved significantly, SSRI may have produced a larger effect than placebo. For the majority of indices measured the therapeutic groups appear to be equally effective to placebo; which may indicate a regression towards the mean, a natural history improvement amongst the cohort of individuals being observed or mainly a placebo response related to the intervention, manner and environment in which the intervention was provided and the patient-clinician interaction established during the study period.

The implication for the clinician is that improvement, to some extent, is independent of the actual therapy provided but may instead rely more fundamentally upon the relationship established between patient and clinician. However, such findings could engender complacency in planning management strategies. Such an assumption is of course, also potentially dangerous since differential diagnosis or underlying pathology could be overlooked. The existence and diagnosis of secondary pathology was demonstrated within this study population. Uninformed or bland reassurance

could be detrimental in prolonging the correct diagnosis or delaying appropriate treatment. However, well informed reassurance and explanation from a specialist, following a careful history and examination, reduces fear and anxiety and therefore increases the patient's ability to accept the diagnosis. The doctor-patient relationship can therefore has a very positive influence, in providing an active impetus to the healing process. This in turn acts as a foundation upon which the patient can then more readily collaborate with the clinician in learning coping strategies and self-care management.

The implications for policy holders also requires consideration. Referral of patients to a specialist centre, who on average had experienced pain for a mean 3 years, showed significant improvement in their condition which was maintained, at up to a year post therapy, when reviewed within a specialist environment. Superior efficacy of medication, splint or combined therapy in the management of TMD was not elucidated. This does not necessarily suggest equivalence but also does not give a clear indication as to the most appropriate therapeutic approach. One must therefore consider which intervention was the most cost effective in the short and long term and also consider the profound placebo effect of specialist intervention.

An estimate of costs indicates a very similar economic outlay. A monthly supply of Fluoxetine is £30, hence £ 90 when given for three months. Alternatively, laboratory fees and impression material for a hard acrylic bite guard are similar, in the region of £90. Both groups of patients require regular follow-up, the latter requiring more time consuming fitting and adjustment of the appliance. A simple cost analysis does not therefore favourably distinguish one group from another.

All groups revealed significant improvement in the short-term at the three month completion of therapy and also during the six and nine month follow up. Long-term follow up at 10 years is being considered for this study and would be a useful tool to

explore if either group show a significant prolonged therapeutic effect. In the meantime, the second consideration is not necessarily what treatment should be provided but by whom should patients be managed?

One popular approach is to consider that GDP's and GP's are appropriately trained and equipped to deal with both acute and chronic TMD within the primary care setting, hence reducing hospital waiting lists and allowing the hospital specialist to concentrate on complex and intransigent cases. However there are several as yet unresolved, fundamental criticisms to this approach. Firstly, lack of remuneration and time available to GDP's to undertake such care within an already hectic NHS practice. Time constraints could be problematic since an inadequate history may mask the underlying cause of pain. Treating the superficial symptoms rather than the whole individual could be detrimental in the long-term. The pain may become more entrenched requiring far greater reserves of NHS time and increased utilization of health care resources for further chronic pain conditions.

In reality, chronic TMD is still considered by many a specialist field, reflected in the vast number of referrals from primary, secondary and tertiary care settings. Requests range from queries or confirmation of diagnosis, secondary opinions and advice on management or requests for further management within a specialist environment. Education at both the undergraduate and postgraduate level including lectures, seminars, practical courses, journal articles and on-line CPD resources can all aid in the dissemination of information to the primary care sector. Conversely, an information overload particularly from the internet can provide conflicting and confusing advice. The evidence based medicine approach to TMD can be difficult to disentangle for both the busy practitioner and patient. This can lead to unnecessary orthodontics and occlusal rehabilitation which still occurs on a far too regular basis. Inappropriate care can be detrimental to the healing process and can sometimes lead

to worsening of the TMD pain which becomes more recalcitrant to therapy and requires greater reserves of specialist time and effort in the long-term. Specialists do therefore have a role, not only in providing EBM education programmes but also in providing the necessary informed advice, both to the patient and the primary care practitioner, to relay the correct diagnosis, eliminating differential diagnoses and suggesting appropriate management.

In particular, there is a need for the patients to actively participate in their care, to learn to self manage their own chronic pain, (VonKorff, Glasgow and Sharpe,2002). To successfully achieve this aim one must first establish the patient's current level of knowledge, understanding and beliefs. Their satisfaction with the diagnosis given and previous treatment provided should be gauged together with the current impact of pain on quality of life, their expectations of treatment and overall goals. In collaboration with the patient, a positive and achievable, individually tailored, self-management plan can then be established. The Department of Health, 2002, "expert patient" programme can be a useful, adjunctive tool for encouraging patient education and self care. This includes the development of written and electronic self-care patient information, telephone guidance, the promotion of self-care protocols, national and local training programmes. A proposed scheme of TMD management utilizing both primary and secondary care resources has been illustrated in figure 76. Where facilities allow, a multidisciplinary pain team can be beneficial for the more complex TMD or mixed oro-facial pains. The group can be composed of a range of specialists for instance: ENT, Neurology, Psychiatry, Dental, Maxillofacial and Oral Surgery. The correct informed advice on management is known to help 40-60% of TMD patients (White and Schiffman, 1991). A brief survey of patients attending for TMD consultation appointments at the EDH, 2004, revealed favourable comments, confirming patients acknowledged their condition was being taken seriously, within

a specialist environment, which enhanced a therapeutic response. In addition, the referring practitioner can be provided with an appropriate level of support and advice by letter or additional e-mail or telephone contact. The majority of patients can then be referred back to and managed by the primary care practitioner, who can provide the suitable continuity of care required, sometimes extending over several years. Delegation of management to appropriately trained hygienist or therapist may also be appropriate when allocated a suitable length of time for the teaching of TMD conservative advice and self-care management skills. Involving Dental hygienists has previously been shown to be an effective use of resources, Magnusson et al, 1999 and Drangsholt, 1999. Ultimately, long-term management for a large proportion of patients with TMD could be managed within the primary care setting. However, some patients; within the EDH referral population an estimated third; require therapeutic intervention within the hospital environment. This may be a series of 3-4 appointments for occlusal appliance therapy or medical therapy before discharge to the primary care setting. A small minority of patients require utilization of other resources available within the hospital notably those with pathology necessitating arthroscopic surgical intervention or those with psychological distress or dysfunction requiring liaison psychiatric assistance or psychological intervention particularly CBT individually or within groups.

Regardless of therapeutic mode, six month or yearly review may sometimes be required to ensure damage limitation for those in need of occasional reassurance and or monitoring of ongoing therapy, particularly those otherwise at risk of seeking inappropriate, irreversible treatment elsewhere. Not discharging certain patients too early can therefore prevent or avoid relapse or escalation in pain which could require far greater resources to control at a future point in time. Guidelines for management are important provided they simply remain guidelines so that clinicians within the confines

of evidence based practice are able to provide and adapt treatment to the benefit of the individual patient.

Another important consideration is the research component of TMD. Unless the condition of TMD can be investigated further in a specialised pain unit one can never unravel the complexity of subgroups and their most appropriate management. However, once the aetiology and risk factors have been fully elucidated then patients can be confidently seen outside a specialist environment. In the meantime it would be almost impossible to monitor patients in the primary care setting not enrolled in a research programme. This would result in lost opportunities to further our understanding of this condition and would be detrimental to the future care of our patients.

10.6 UNRESOLVED QUESTIONS, RECOMMENDATIONS AND FUTURE RESEARCH

10.6.1 Occlusal appliance therapy

The hard occlusal appliance, although efficacious both alone and in combination with medication, did not show superiority to medication or indeed placebo therapy. One possibility is that other types of occlusal appliance may have additional benefits in terms of ease of fabrication and usage. A comparison of resilient versus hard occlusal appliances could be considered, particularly when one appreciates the influence of the cognitive awareness theory on splint action and the reduced costs involved in construction. A recent study suggested self-care treatment alone or in combination with soft and hard occlusal appliances resulted in all patients improving over time, Truelove et al, 2006. However, a more detailed study of the effect of different appliances could still be undertaken.

From clinical experience, current practice and the confirmation of this recent study, it remains prudent to always introduce patients to the most conservative treatment measure of self-care advice initially, as indicated in the proposed TMD management programme, (figure 76). It may become clearer following subgroup analysis which patients benefit most readily from the additional intervention of occlusal appliances. However, at present one could consider those with a clenching or bruxism habit sometimes with observable damage to the intra oral tissues and or symptoms of TMD on waking. When or if occlusal appliance therapy is indicated in a particular individual, then, from the perspective of patient comfort, cost, time, ease of fabrication, adjustment and seemingly equivalent efficacy, a resilient soft appliance should be considered before embarking on the construction of a hard flat plane appliance.

10.6.2 Antidepressant medication

Superior efficacy of medical therapy to occlusal therapy was not demonstrated. This may suggest equivalence in efficacy or may also have been due to the choice of medication, an SSRI rather than a TCA. If sleep bruxism does play a role in TMD perpetuation then the SSRI may inadvertently have aggravated this condition rather than the more sedative TCA, as discussed in detail in Chapter VII. However, the SSRI did reveal superior efficacy to placebo, >50% pain relief at three months, so some individuals clearly benefited from the medication. The subgroup analysis suggested those suffering from depression and initially high levels of pain may respond more readily to the medical therapy although this did not reach significance between groups but may warrant further investigation. Interestingly, MPI life control and affective distress did appear to decrease most significantly amongst the SSRI group. Where medication is indicated for a patient and there is a significant sleep

disturbance a TCA may still be the drug of choice. Otherwise, an SSRI can be beneficial in some patients, particularly when wishing to avoid the antimuscarinic side effects of the TCA. A direct comparison of a TCA and an SSRI in TMD, utilizing a RCT design has not been undertaken and remains an unresolved issue which would be very interesting to determine. However, the influence of clinical and psychosocial subgroups of TMD on outcome, together with covariates related to high initial levels of pain, depression, alterations in sleep pattern and co-morbid pain conditions would need to be incorporated into any analysis. Liu et al,2005 suggest a two stage trial to first distinguish 'responders' and then a second trial aimed at this group would increase the power of efficacy and require fewer participants with treatment aimed at a specified population.

In designing TMD clinical trials for the future, the recognition of the numerous covariate effects would enable researchers to identify individual responders or subpopulations that will react favourably to therapy; providing both more efficient and cost effective research trials and treatment.

Future studies need to focus on subgroup analysis in an attempt to extricate the various sub-entities within the conglomerate of TMD. For example more stringent subgroup analysis, not only in relation to arthralgic and myalgic components of TMD but also for example utilizing this and other TMD cohorts for MPI mapping into chronic pain groups proposed by Rudy and Turk, 1987 or utilizing the chronic graded pain scale (Forsell et al,) .This may help to elucidate patterns of therapeutic response amongst those with specific clinical and psychosocial pain characteristics. Further covariates are numerous but may include: sleep, nocturnal bruxism and clenching, level of depression, co-morbid pain conditions particularly TTH, as well as the more unusual including perhaps the season in which research is undertaken for example winter versus summer, the influence of the clinician's character, study

environment and most importantly issues related to patient levels of distress, dysfunction and quality of life.

Overall the strengths of the study are those of a well conducted RCT with acceptable internal and external validity within the sphere of EBM. The study was conducted before the advent of the recent explosion in comprehensive guidelines on conducting RCT's but fulfils the criteria outlined by CONSORT. Methodological flaws would include the information sheet and consent form which would now have been written in a much more detailed manner. However, the patients were not disadvantaged by this but were given clear, coherent information throughout the course of the study.

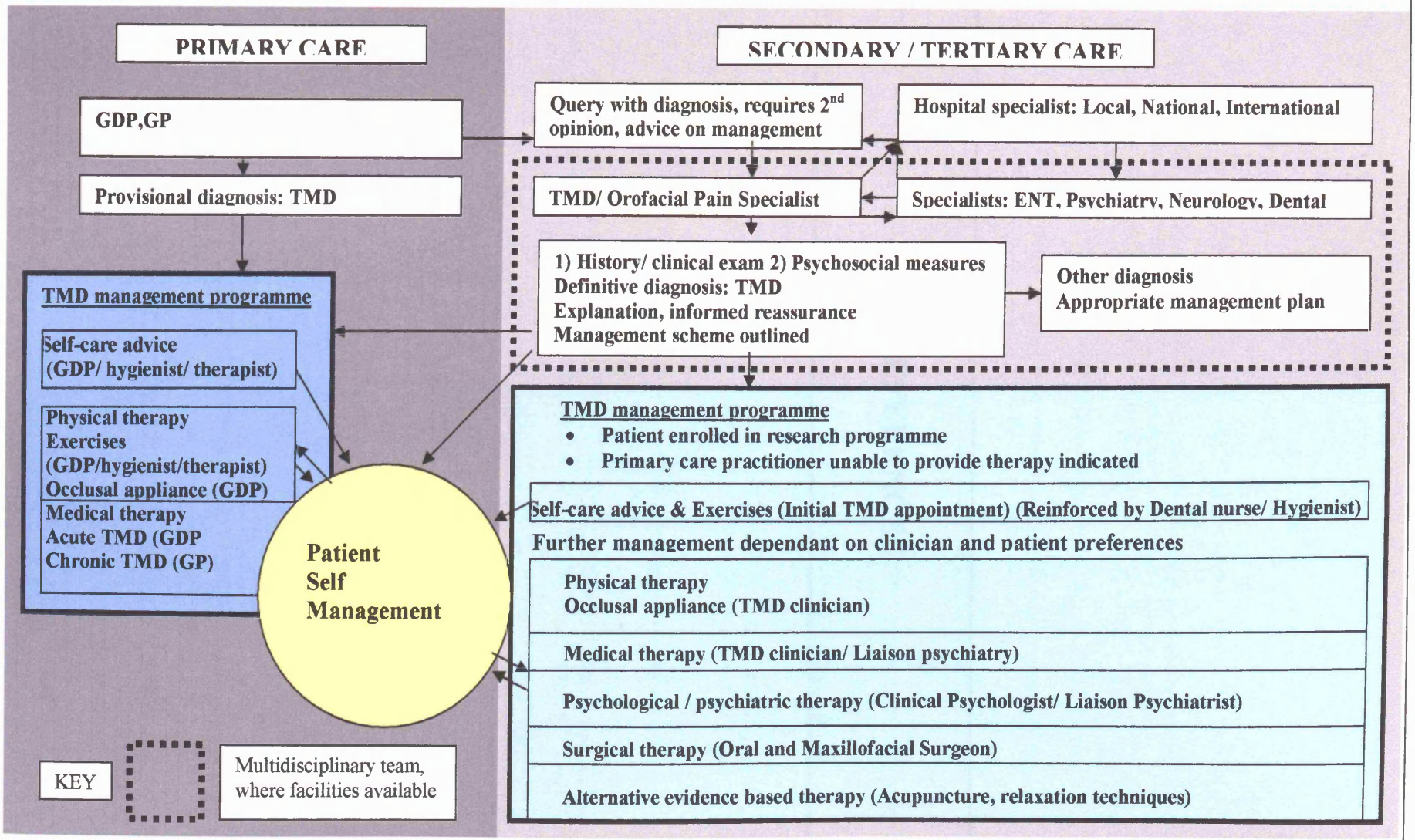
In future studies, ideally additional personnel would be required including at least three calibrated clinicians one providing treatment, one assessing adverse effects and compliance and the third assessing treatment outcome, blind not only to drug therapy but to all therapeutic interventions, so decreasing the likelihood of detection bias.

In relation to compliance, rather than relying on self report and pill counts, future studies could utilise some of the newer techniques discussed in Chapter IX. The simplest would be diary cards, whilst online internet records, electronic pill counters or regular blood tests could all be considered.

Although the length of time patients were followed up post therapy was a strength of this study, it is envisaged that further follow-up will be undertaken with this particular cohort to determine long term follow-up at 10 years. Patient recall and attendance for a clinical review appointment, although useful in physically assessing patient signs of TMD for comparison to baseline and end of therapy, is clearly expensive and largely impractical. A questionnaire or telephone follow-up of self report symptoms is much more cost effective in terms of both patient and clinician time.

Further RCT are necessary to continually improve our knowledge and understanding of the field particularly in relation to sub-group analysis. Global interaction and cooperation is also required to pool resources, research knowledge and capabilities on the epidemiology, aetiology, diagnosis and management which in turn will lead to a better understanding of the field.

Figure 76: **MANAGEMENT OF TMD**



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APPENDICES

Appendix 1 – Consent form for the Facial Arthromyalgia study

EASTMAN DENTAL INSTITUTE
FOR ORAL HEALTH CARE SCIENCES
University of London

FACIAL ARTHROMYALGIA (TMD) STUDY

JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

CONSENT FORM

- I agree to take part in this study on facial arthromyalgia treatment.
- I have received and read the information sheet explaining the study.
- I understand I shall be asked to attend the Eastman Dental Hospital at regular intervals, approximately six times, over a period of three months and to attend follow up sessions over the nine months immediately following my treatment.
- I shall be asked to fill in a number of questionnaires as part of the study.
- I understand I cannot choose which treatment I have but that I can withdraw from the treatment at any time.

SIGNED **DATE**.....

Patient:.....

Please print in
capital letters .....

Interviewer:.....

Please print in
capital letters.....

Witness:.....

(Member of Facial Arthromyalgia team)

Position:.....

Appendix 2 – Information sheet for the Facial Arthromyalgia study

EASTMAN DENTAL INSTITUTE
FOR ORAL HEALTH CARE SCIENCES
University of London

FACIAL ARTHROMYALGIA (TMD) STUDY

JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

INFORMATION SHEET

What is Facial Arthromyalgia?

All our investigations have shown that you have no sign of disease in your joints.
Most toothache and other dental problems are fairly straight forward and respond to standard treatment.Other pains may persist for a time changing in intensity according to how you feel.Treatment is varied and different individuals may respond to:taking medication,wearing a splint,stress management or learning how to relax.

This leaflet tells you more about the pain you have and how this project may help you.
The most likely diagnosis of your pain is a condition known as:-
Facial Arthromyalgia (Temporomandibular joint dysfunction syndrome)
This is a continuous or intermittent dull ache with or without occasional severe attacks affecting your jaw joint and its muscles. You may also experience clicking noises in the joint,difficulty opening the mouth and tenderness or spasm in the jaw muscles in the immediate area around the joint or extending into the head and down into the neck.
Ear symptoms of a sense of fullness,buzzing,popping and dizzieness may also occur.

Study into Facial Arthromyalgia management.

This study aims to find out the most effective means of treatment for this condition.It is a trial comparing Medical and Physical splint therapy alone or together.
Medical therapy involves taking one of two tablets being used in the trial.Antidepressants are not given because we think you are depressed but because it has been shown that these drugs help relieve pain and are not addictive.
Physical splint therapy involves wearing an individually made acrylic appliance on the upper teeth in order to relieve the joint and muscle pain.
All those taking part in the study will be randomly allocated to one of the treatment groups.
If you have any further questions about the study,a member of the research team will be glad to answer any queries.

Appendix 3 – Letter to general medical and dental practitioner

To inform them of their patient's potential participation in the Facial Arthromyalgia study

EASTMAN DENTAL INSTITUTE
FOR ORAL HEALTH CARE SCIENCES
University of London

FACIAL ARTHROMYALGIA (TMD) STUDY

JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

Professor Malcolm Harris
Dr. Charlotte Feinmann
Mr. Richard Ibbetson
Miss Rachel Leeson
Mr. Paul O'Neilly

Re:_____, **DOB:**_____,

Address:_____, **Ref. No.:**_____,

_____,

_____.

Dear

Thank you for referring the above patient whom I saw on behalf of the Facial Arthromyalgia project team on_____.

CO:

HPC:

PMH:

SH:

Clinical Examination:

Radiographic Examination:

A diagnosis of Facial Arthromyalgia (TMJ dysfunction syndrome) was made. At present the department is undertaking a project involving patients with this complaint and the above patient has very kindly agreed to take part in this trial.

The aim of the study is to compare the effectiveness of Medical, Physical or combined Medical and Physical therapy in the management of this condition.

The study is a randomised (double blind for drug treatment) controlled trial in which patients will be allocated to one of four groups : fluoxetine (Prozac), placebo, full coverage occlusal splint or splint plus fluoxetine.

The initial duration of the study is three months, during which time there are regular review appointments to assess the treatment progress and care of the individual. There are then two follow up appointments at three month intervals. The patient would of course be able to withdraw from the treatment at any time during the course of the trial.

Your patient has shown interest in taking part in this project. I would therefore be grateful if you could let me know if there is any reason you would not be happy for this patient to enter into the trial.
Thank you for your co-operation and help in this matter.

The department will of course endeavour to keep you informed of the progress of this patient, whilst receiving treatment under our care.

Yours sincerely,

Miss Rachel Leeson,
REGISTRAR,
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY.

Appendix 4 – Letter to Heads of Department within the Eastman Dental Hospital requesting referral of patients.

- **Action flow chart to illustrate proposed attendance plan for selected patients**

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Professor Malcolm Harris
Mr. Richard Ibbetson
Dr. Charlotte Feinmann
Miss Rachel Leeson
Mr. Paul O'Neilly

Dear

The Departments of Conservative Dentistry and Maxillofacial and Oral Surgery are jointly undertaking a research project into temperomandibular joint dysfunction (Facial Arthromyalgia). Patients selected from the Conservation, Periodontal and Prosthetics departments will be entering a trial to compare the use of a full coverage occlusal splint versus medical management of the condition.

I would be most grateful if you could collect patients referred with pain in one or both TMJs, with or without clicking, limitation in opening or tenderness in the associated musculature.

Unsuitable patients are :-

- those with significant untreated dental disease.
- those undergoing extensive or complex restorative treatment
- those where history of the joint condition appears long and intractable

Suitable patients should have :-

- reasonable plaque control .
- sufficient teeth to allow construction of a stable occlusal splint.

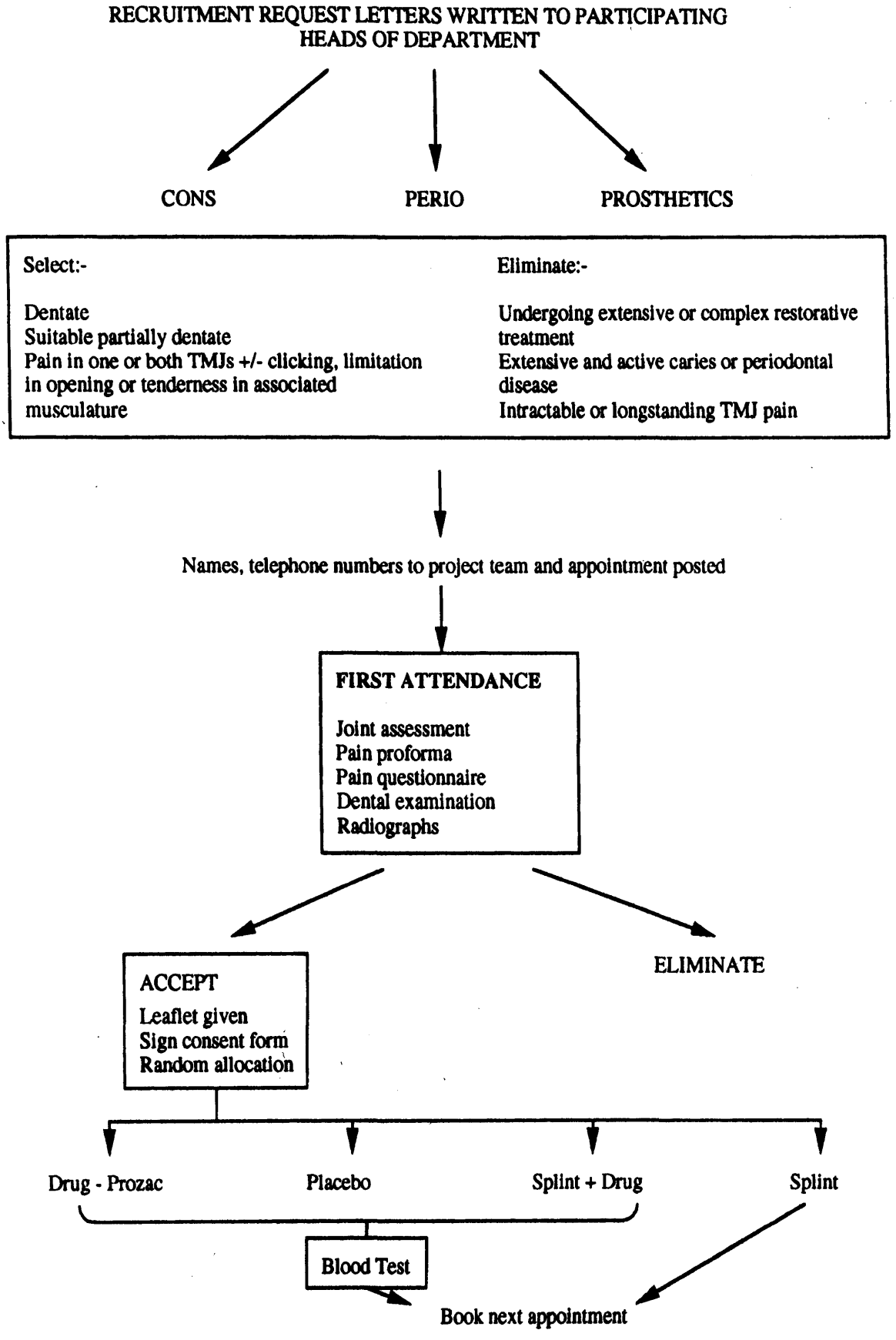
We shall then send the selected patients appointments for a joint assessment and information on the project.

Thank you very much for your help in this matter.

Yours sincerely,

Miss Rachel Leeson,
REGISTRAR,
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY.

ACTION FLOW CHART



Appendix 5 – A reminder and thank you letter to participating general dental practitioners

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University of London

FACIAL ARTHROMYALGIA (TMD) STUDY

JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

Professor Malcolm Harris
Dr. Charlotte Feinmann
Mr. Richard Ibbetson
Miss Rachel Leeson
Mr. Paul O'Neilly

Dear Sir/ Madam,

Further to our letter in January/ February, 1995, I am writing to remind you of the Temporomandibular joint dysfunction (Facial Arthromyalgia) research project, presently being undertaken at the Eastman Dental Hospital.

Patients with pain in one or both TMJ's, with or without clicking, limitation in opening or tenderness in associated musculature would be gratefully received. However, those patients who have had extensive treatment for this condition, will not be suitable for our trial. Treatment includes comparison of full coverage occlusal splint with medical management, which is randomly allocated to the patient.

May I take this opportunity to thank you for patients you have already referred. Please do not hesitate to send us further cases.
Referral address: Miss Rachel Leeson,
Oral Surgery Department
Eastman Dental Hospital

Thank you for your help in this study.

Yours sincerely,

Miss Rachel Leeson,
REGISTRAR,
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY.

Appendix 6 – Appointment letters

- **New patient letter for an initial assessment**
- **Letter for a further appointment following failed attendance**
- **Reminder letter for three month follow-up appointment**
- **Reminder letter for six month follow-up appointment**
- **Reminder letter for nine month follow-up appointment**

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JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

Professor Malcolm Harris
Mr. Richard Ibbetson
Dr. Charlotte Feinmann
Miss Rachel Leeson
Mr. Paul O'Neilly

Dear

An appointment has been made for you to attend our clinic for an initial assessment

on : _____ at : _____.

location : _____.

This clinic is for patients with jaw joint and muscle problems.

In order to make a diagnosis we need to see you for a long first appointment. A detailed history is recorded, a dental examination is carried out and X-rays are taken. You will also be asked to fill in a pain questionnaire.

At present the Eastman Dental Hospital is carrying out a study into the most effective treatment of pain associated with the jaw joint, comparing the use of bite splints and medication, both of which have had reported success in the past.

If, after your first appointment it is felt you would be a suitable candidate for this study the project will be explained to you in more detail and a leaflet given to you.

If you are willing to participate you will be randomly allocated to one of the groups. It will be necessary for you to be available for approximately six appointments on a Thursday over a period of three months and follow up appointments arranged after a further three months and six months time.

We look forward to meeting you at the first appointment. If you are unable to attend **please ring to cancel or change the appointment time** if necessary.

Thank you for your co-operation.

Yours sincerely,

Eastman Facial Arthromyalgia Project
Department of Oral and Maxillofacial Surgery.

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Professor Malcolm Harris
Dr. Charlotte Feinmann
Mr. Richard Ibbetson
Miss Rachel Leeson
Mr. Paul O'Neilly

Date:_____.

Hospital No:_____.

Dear _____,

As you failed to attend your appointment on _____,
I am writing to ask if you would like to be given another appointment on the Facial Arthromyalgia clinic.

We have appointments available for a Tuesday morning between 8:30am - 12:30pm and on a Thursday afternoon between 2:00pm and 4:30pm. If you would like to arrange an apppointment during these times, please do not hesitate to contact me on

Looking forward to meeting you.

Yours sincerely,

_____.

Eastman Facial Arthromyalgia Project,
Department of Oral and Maxillofacial Surgery.

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Professor Malcolm Harris
Dr. Charlotte Feinmann
Mr. Richard Ibbetson
Miss Rachel Leeson
Mr. Paul O'Neilly

Date:_____.

Hospital no:_____.

Dear _____,

This is just to confirm that you are due for your 3 month review appointment on:

_____at_____.

At this appointment you will be asked to fill out a questionnaire on your progress throughout this trial. If you are unble to make this appointment or have any queries please contact us on .

Yours sincerely,

_____.

Eastman Facial Arthromyalgia Project,
Joint Department of Oral and Maxillofacial Surgery.

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JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

Professor Malcolm Harris
Dr. Charlotte Feinmann
Mr. Richard Ibbetson
Miss Rachel Leeson
Mr. Paul O'Neilly

Date:_____.

Hospital no:_____.

Dear _____,

This is just to confirm that you are due for your 6 month review appointment on:

_____at_____.

At this appointment you will be asked to fill out a questionnaire on your progress throughout this trial. If you are unble to make this appointment or have any queries please contact us on).

Yours sincerely,

_____.

Eastman Facial Arthromyalgia Project,
Joint Department of Oral and Maxillofacial Surgery.

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University of London

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JOINT RESEARCH OF THE DEPARTMENTS OF MAXILLOFACIAL AND ORAL SURGERY AND CONSERVATIVE DENTISTRY

Professor Malcolm Harris
Dr. Charlotte Feinmann
Mr. Richard Ibbetson
Miss Rachel Leeson
Mr. Paul O'Neilly

Date:_____.

Hospital no:_____.

Dear _____,

This is just to confirm that you are due for your 9 month review appointment on:

_____at_____.

At this appointment you will be asked to fill out a questionnaire on your progress throughout this trial. If you are unble to make this appointment or have any queries please contact us on).

Yours sincerely,

_____.

Eastman Facial Arthromyalgia Project,
Joint Department of Oral and Maxillofacial Surgery.

Appendix 7 – Self-report pain questionnaires

- **The Multidimensional Pain Inventory (MPI)**
- **The McGill Short form Pain Questionnaire (SF-MPQ)**
- **The Kellner Illness Attitude Scale (Kellner)**
- **The Beck Depression Inventory (BDI)**

MULTIDIMENSIONAL PAIN INVENTORY

Date:_____.

Name:_____.
First Initials Surname/Family name

Age:_____.

Sex:_____.

Main site of pain:_____.

When did pain start?:_____.

Instructions

An important part of our evaluation includes examination of pain from your perspective because you know your pain better than anyone else. The following questions are designed to help us learn more about your pain and how it affects your life.

Under each question is a scale to mark your answer. Read each question carefully and then circle a number on the scale under that question to indicate how specific question applies to you. An example may help you to understand better how you should answer these questions.

Example

How nervous are you when you ride in a car when the traffic is heavy?

0	1	2	3	4	5	6
Not at all nervous						Extremely nervous

If you are not at all nervous when riding in a car in heavy traffic, you would want to circle the number 0. If you are very nervous when riding in a car in heavy traffic, you want to circle the number 6. Lower numbers would be used for less nervousness, and higher numbers for more nervousness.

Go to next page

Section I

1 Rate the level of pain at the present moment.

0	1	2	3	4	5	6
No pain						Very intense pain

2 In general, how much does your pain interfere with your day to day activities?

0	1	2	3	4	5	6
No interference						Extreme interference

3 Since the time your pain began, how much has your pain changed your ability to work? ___. Tick here if you have retired for reasons other than your pain.

0	1	2	3	4	5	6
No change						Extreme change

4 How much has your pain changed the amount of satisfaction or enjoyment you get from taking part in social and recreational activities?

0	1	2	3	4	5	6
No change						Extreme change

5 How supportive is your spouse of significant other person to you in relation to your pain?

0	1	2	3	4	5	6
Not at all supportive						Extremely supportive

6 Rate your overall mood during the past week.

0	1	2	3	4	5	6
Extremely low						Extremely high

7 How much has your pain interfered with your ability to get enough sleep?

0	1	2	3	4	5	6
No interference						Extreme interference

8 On average, how severe has your pain been during the last week?

0	1	2	3	4	5	6
Not at all severe						Extremely severe

9 How able are you to predict when your pain will start, get better, or get worse?

0	1	2	3	4	5	6
Not at all able to predict						Very able to predict

10 How much has your pain changed your ability to take part in recreational and other social activities?

0	1	2	3	4	5	6
No change						Extreme change

11 How much do you limit your activities in order to keep your pain from getting worse?

0	1	2	3	4	5	6
Not at all						Very much

12 How much has your pain changed the amount of satisfaction or enjoyment you get from your family-related activities?

0	1	2	3	4	5	6
No change						Extreme change

13 How worried about you is your spouse or significant other person because of your pain?

0	1	2	3	4	5	6
Not at all worried						Extremely worried

14 During the <u>past week</u> how much control do you feel that you have had over your life?

0	1	2	3	4	5	6
No control						Extreme control

15 On an average day, how much does your pain vary (increase or decrease)?

0	1	2	3	4	5	6
Remains the same						Changes a lot

16 How much suffering do you experience because of your pain?

0	1	2	3	4	5	6
No suffering						Extreme suffering

17 How often are you able to do something that helps reduce your pain?

0	1	2	3	4	5	6
Never						Very often

18 How much has your pain changed your relationship with your spouse, family, or significant other?

0	1	2	3	4	5	6
No change						Extreme change

19 How much has your pain changed the amount of satisfaction or enjoyment you get from work?____ Tick here if you are not working at present.

0	1	2	3	4	5	6
No change						Extreme change

20 How attentive is your spouse or significant other person to you because of your pain?

0	1	2	3	4	5	6
Not at all attentive						Extremely attentive

21 During the <u>past week</u> how much do you feel that you've been able to deal with your problems?

0	1	2	3	4	5	6
Not at all well						Extremely well

22 How much control do you feel you have over your pain?

0	1	2	3	4	5	6
No control at all						A great deal of control

23 How much has your pain changed your ability to do household chores?

0	1	2	3	4	5	6
No change						Extreme change

24 During the past week, how successful were you at coping with stressful situations in your life?

0	1	2	3	4	5	6
Not at all successful						Extremely successful

25 How much has your pain interfered with your ability to plan activities?

0	1	2	3	4	5	6
No change						Extreme change

26 During the past week, how irritable have you been?

0	1	2	3	4	5	6
Not at all irritable						Extremely irritable

27 How much has your pain changed or interfered with your friendships with people other than your family?

0	1	2	3	4	5	6
No change						Extreme change

28 During the past week how tense or anxious have you been?

0	1	2	3	4	5	6
Not at all tense or anxious						Extremely tense or anxious

Section II

In this section, we are interested in knowing how your spouse or significant other person responds to you when he or she knows that you are in pain. On the scale listed below each question, circle a number to indicate how often your spouse or significant other person responds to you in that particular way when you are in pain. Please answer all of the 14 questions.

1 Ignores me.

0 1 2 3 4 5 6
Never Very often

2 Asks me what he/she can do to help.

0 1 2 3 4 5 6
Never Very often

3 Reads to me.

0 1 2 3 4 5 6
Never Very often

4 Gets irritated with me.

0 1 2 3 4 5 6
Never Very often

5 Takes over my jobs or duties.

0 1 2 3 4 5 6
Never Very often

6 Talks to me about something else to take my mind off the pain.

0 1 2 3 4 5 6
Never Very often

7 Gets frustrated with me.

0 1 2 3 4 5 6
Never Very often

8 Tries to get me to rest.

0 1 2 3 4 5 6
Never Very often

9 Tries to involve me in some activity.

0 1 2 3 4 5 6
Never Very often

10 Gets angry with me.

0 1 2 3 4 5 6
Never Very often

11 Gets me pain medication.

0 1 2 3 4 5 6
Never Very often

12 Encourages me to work on a hobby.

0 1 2 3 4 5 6
Never Very often

13 Gets me something to eat or drink.

0 1 2 3 4 5 6
Never Very often

14 Turns the TV on to take my mind off the pain.

0 1 2 3 4 5 6
Never Very often

Section III

Listed below are 24 common activities. Please indicate how often you would do each of these by circling a number on the scale below each activity Please complete all 24 questions

1 Wash dishes.

0 1 2 3 4 5 6
Never Very often

2 Mow the lawn ___ Tick here if you do not have a lawn to mow.

0 1 2 3 4 5 6
Never Very Often

3 Go out to eat.

0 1 2 3 4 5 6
Never Very often

4 Play cards or other games.

0 1 2 3 4 5 6
Never Very often

5 Go grocery shopping.

0 1 2 3 4 5 6
Never Very often

6 Work in the garden ___ Tick here if you do not have a garden.

0 1 2 3 4 5 6
Never Very often

7 Go to a movie.

0 1 2 3 4 5 6
Never Very often

15 Take a trip.

0 1 2 3 4 5 6
Never Very often

16 Go to a park or beach.

0 1 2 3 4 5 6
Never Very often

17 Do the laundry.

0 1 2 3 4 5 6
Never Very often

18 Work on a needed household repair.

0 1 2 3 4 5 6
Never Very often

SHORT FORM McGILL PAIN QUESTIONNAIRE

Section 1.

Please answer this section with reference to the pain you usually suffer from. If a word does not describe your pain, tick "NONE" next to that word. If a word does describe your pain, indicate whether you experience this sensation to a "mild", "moderate" or "severe" degree, by ticking next to the relevant word. Please make sure you place a tick in one of the categories for each word.

	NONE	MILD	MODERATE	SEVERE
THROBBING	0)_____	1)_____	2)_____	3)_____
SHOOTING	0)_____	1)_____	2)_____	3)_____
STABBING	0)_____	1)_____	2)_____	3)_____
SHARP	0)_____	1)_____	2)_____	3)_____
CRAMPING	0)_____	1)_____	2)_____	3)_____
GNAWING	0)_____	1)_____	2)_____	3)_____
HOT-BURNING	0)_____	1)_____	2)_____	3)_____
ACHING	0)_____	1)_____	2)_____	3)_____
HEAVY	0)_____	1)_____	2)_____	3)_____
TENDER	0)_____	1)_____	2)_____	3)_____
SPLITTING	0)_____	1)_____	2)_____	3)_____
TIRING-EXHAUSTING	0)_____	1)_____	2)_____	3)_____
SICKENING	0)_____	1)_____	2)_____	3)_____
FEARFUL	0)_____	1)_____	2)_____	3)_____
PUNISHING-CRUEL	0)_____	1)_____	2)_____	3)_____

Section 2.

Please answer this section with reference to the pain you have **RIGHT AT THIS MOMENT.**

A) Draw a line through the scale below to indicate where your pain is at the moment. (e.g. ———/———), imagining that the line indicates a ladder going from no pain to the worst possible pain.

NO PAIN		WORST POSSIBLE PAIN

B) Tick next to ONE of the following words to indicate how intense your pain is at the moment.

0	NO PAIN	_____
1	MILD	_____
2	DISCOMFORTING	_____
3	DISTRESSING	_____
4	HORRIBLE	_____
5	EXCRUCIATING	_____

Illness Attitudes Scale

Kellner

No	Rarely	Sometimes	Often	Most of the time
1	2	3	4	5

1. Do you believe that you have a physical disease, but the doctors have not diagnosed it correctly?

   1 2 3 4 5

2. When your doctor tells you that you have no physical disease, do you refuse to believe him/her?

   1 2 3 4 5

3. When you have been told by the doctor what he found, do you soon begin to believe that you may have developed a new illness?

   1 2 3 4 5

4. Are you afraid that you may have cancer?

   1 2 3 4 5

5. Are you afraid that you may have heart disease?

   1 2 3 4 5

6. Are you afraid that you may have another serious illness?

   1 2 3 4 5

BDI

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0,1,2 or 3) next to the one statement in each group which best describes the way you have been feeling the past week and today. If several statements within a group seem to apply equally well, circle each one.
Be sure to read all the statements in each group before making your choice.

1. 0 I do not feel sad
   1 I feel sad
   2 I am sad all the time and I can't snap out of it
   3 I am so sad or unhappy that I can't stand it

2. 0 I am not particularly discouraged about the future
   1 I feel discouraged about the future
   2 I feel that I have nothing to look forward to
   3 I feel that the future is hopeless and that things can't improve

3. 0 I do not feel like a failure
   1 I feel I have failed more than the average person
   2 As I look back on my life all I can see is a lot of failures
   3 I feel I am a complete failure as a person

4. 0 I get as much satisfaction out of things as I used to
   1 I don't enjoy things the way I used to
   2 I don't get real satisfaction out of anything anymore
   3 I am dissatisfied or bored with everything

5. 0 I don't feel particularly guilty
   1 I feel guilty a good part of the time
   2 I feel quite guilty most of the time
   3 I feel guilty all of the time

6. 0 I don't feel I am being punished
   1 I feel I may be punished
   2 I expect to be punished
   3 I feel I am being punished

7.	0	I don't feel disappointed in myself
	1	I am disappointed in myself
	2	I am disgusted with myself
	3	I hate myself
8.	0	I don't feel I am any worse off than anybody else
	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9.	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself but I would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10.	0	I don't cry any more than usual
	1	I cry more now than I used to
	2	I cry all the time now
	3	I used to be able to cry but now I can't cry even though I want to
11.	0	I am no more irritated now than I ever am
	1	I get annoyed or irritated more easily than I used to
	2	I feel irritated all the time now
	3	I don't get irritated at all by the things that used to irritate me
12.	0	I have not lost interest in other people
	1	I am less interested in other people than I used to be
	2	I have lost most of my interest in other people
	3	I have lost all of my interest in other people
13.	0	I make decisions as well as I ever could
	1	I put off making decisions more than I used to
	2	I have greater difficulty in making decisions than before
	3	I can't make decisions anymore
14	0	I don't feel I look any worse than I used to
	1	I am worried that I am looking old or unattractive
	2	I feel that there are permanent changes to my appearance that make me look unattractive
	3	I believe that I look ugly

15 0 I can work about as well as I used to
1 It takes an extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can't do any work at all

16 0 I can sleep as well as usual
1 I don't sleep as well as I used to
2 I wake up 1-2 hours earlier and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

17. 0 I don't get any more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am to tired to do anything

18. 0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all anymore

19. 0 I haven't lost much weight, if any, lately
1 I have lost more than 5 pounds (2 kilos)
2 I have lost more than 10 pounds (4 kilos)
3 I have lost more than 15 pounds (7 kilos)

I am purposely trying to lose weight by eating less: YES_____ NO_____

20. 0 I am no more worried about my health than usual
1 I am worried about physical problems such as pains, upset stomach or constipation
2 I am very worried about physical problems and it's hard to think of much else
3 I am so worried about my physical problems that I cannot think about anything else

21. 0 I have not noticed any recent changes in my interest in sex
1 I am less interested in sex than I used to be
2 I an much less interested in sex than I used to be
3 I have lost interest in sex completely

Appendix 8 – Eastman Dental Hospital modified Facial Pain proforma

EASTMAN DENTAL INSTITUTE

FACIAL ARTHROMYALGIA
(TMD) STUDY

Study code (1-5)

Patient's study number (6-10)

Patient's Name _____

Date (13-18)
day month year

Hospital number _____ (19-20)

(21-22)

Sex: ..... male$_1$ female$_2$ (24)

Date of birth: ..... (25-30)
day month year

Present marital status: ..... single$_1$ married$_2$ divorced$_3$ widowed$_4$ (31)

Employed: ..... yes$_1$ no$_2$ (33)

Occupation *(if unemployed please state last occupation)*: _____

_____ (34-35)

Referred by: ..... GDP$_1$ GMP$_2$ specialist$_3$ self$_4$ (36)

PRESENTING COMPLAINT AND DURATION

DESCRIPTION OF PAIN

Character

discomfort
dull ache
burning
sharp
stabbing
throbbing

Frequency: never, occasionally, often, always,

Severity

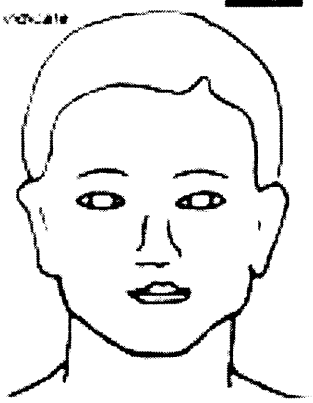
(Please mark the line with a single stroke e.g. —/—)

Nil — unbearable

Site and radiation

left
right
midline
bilateral
Other

Please indicate



TMJ
face
scalp
ears
teeth
jaws and alveolus
palate
gingiva
tongue
neck
Other

Timing

Condition suffered for: weeks, months, years,

Date of onset of present episode: day, month, year

Length of bouts: minutes, hours, days, weeks,

Frequency: daily, weekly, monthly,

Pain-free intervals: days, weeks, months, years,

Worse: am, pm,

Prevents sleeping: yes, no,

Disturbs sleeping: yes, no,

Original precipitating factor(s):

dental ☐ (24)
physical trauma ☐ (25)
infection ☐ (26)
emotional upset ☐ (27)
none ☐ (28)

Provoked by

biting ☐ (29)
chewing ☐ (30)
talking ☐ (31)
yawning ☐ (32)
hot weather ☐ (33)
cold weather ☐ (34)
hot food/drink ☐ (35)
cold food/drink ☐ (36)
cheese ☐ (37)
chocolate ☐ (38)
alcohol ☐ (39)
emotional tension ☐ (40)

Other: _____

_____ (41-42)

Relief

Relieved by

rest ☐ (43)
heat ☐ (44)
chewing ☐ (45)
alcohol ☐ (46)
pressure ☐ (47)
analgesics ☐ (48)

Other: _____

_____ (49-50)

RELATED FACTORS

Sleep ..... no problems$_1$ cannot get to sleep$_2$ disturbed sleep$_3$ early morning wakening$_4$ (51)

Joints

	Right	Left	
clicking	☐	☐	(52-53)
sticking	☐	☐	(54-55)
dislocation	☐	☐	(56-57)

limited opening ☐ (58)
bruxism ☐

Ears

	Right	Left	
popping	☐	☐	(59-60)
buzzing	☐	☐	(61-62)
deafness	☐	☐	(63-64)

Oro-Facial Symptoms

burning tongue ☐ (65)
disturbed taste ☐ (66)
disturbed salivation ☐ (67)
disturbed denture tolerance ☐ (68)
disturbed occlusal comfort ☐ (69)
areas of sensory loss ☐ (70)
areas of paraesthesia ☐ (71)

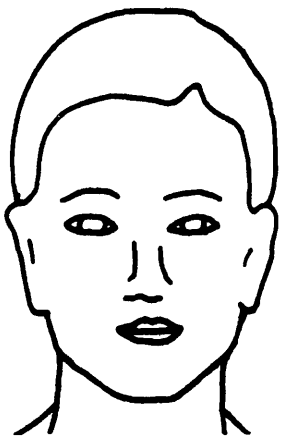
CLINICAL EXAMINATION: ORO-FACIAL

Gross facial asymmetry: ..... yes$_1$ no$_2$ (20)

Swelling
(indicate on diagram): ..... yes$_1$ no$_2$ (26)

Tenderness on palpation
(indicate on diagram): ..... yes$_1$ no$_2$ (25)

Tenderness in ears
(indicate on diagram): ..... yes$_1$ no$_2$ (27)



(21-22)

TMJ

	Right	Left		Right	Left	
tender	☐	☐	(28-29)	sticking ☐	☐	(36-37)
click (opening)	☐	☐	(30-31)	deviation ☐	☐	(38-39)
click (closure)	☐	☐	(32-33)	swelling ☐	☐	(40-41)
crepitus	☐	☐	(34-35)			

interincisal opening (mm) ..... ☐☐ (42-43)

Oral Cavity

Buccal mucosa

—ulcer ..... ☐ (44)

—frictional keratosis ..... ☐ (45)

—abrasion ..... ☐ (46)

—other: _____

_____ ☐☐ (47-48)

Lingual mucosa abnormal: ..... yes$_1$ no$_2$ (49)

Ridging of tongue: ..... yes$_1$ no$_2$ (50)

Ridging of buccal mucosa: ..... yes$_1$ no$_2$ (51)

Saliva: ..... excess$_1$ normal$_2$ reduced$_3$ (52)

Occlusion

Angle class (Dental): ..... 1$_1$ 2I$_2$ 2II$_3$ 3$_4$ (53)

Overbite (mm): ..... ☐☐ (54-55)

Overjet (mm): ..... ☐☐ (56-57)

TEETH *(please circle as appropriate)*

absent

(21-22)

8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 (24-39)
8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 (40-55)

carious cavities

(21-22)

8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 (24-39)
8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 (40-55)

unerupted

(21-22)

8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 (24-39)
8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 (40-55)

PAIN TREATMENT

Seen by

oral surgeon ☐ (37)
GMP ☐ (38)
GDP ☐ (39)
neurologist ☐ (40)
psychiatrist ☐ (41)
ENT surgeon ☐ (42)
Other: _____ (43-44)

Treated with

analgesics ☐ (45)
antibiotics ☐ (46)
tranquillisers ☐ (47)
antidepressants ☐ (48)

fillings ☐ (49)
extirpation of dental pulp ☐ (50)
forceps extraction ☐ (51)
surgical exploration ☐ (52)
surgical extraction ☐ (53)
bite-raising appliance ☐ (54)
occlusal adjustment ☐ (55)
dentures ☐ (56)
exercises ☐ (57)
short-wave diathermy ☐ (58)
osteopathy ☐ (59)
acupuncture ☐ (60)
TMJ injection ☐ (61)
TMJ operation ☐ (62)
Other: _____ (63-64)

PAST HISTORY

MEDICAL HISTORY

headache ☐ (29)
migraine ☐ (30)
neck pain ☐ (31)
back pain ☐ (32)
chest pain ☐ (33)
spastic colon ☐ (34)
abdominal pain ☐ (35)
dysfunctional uterine bleeding ☐ (36)
glandular fever ☐ (37)
pruritus ☐ (38)
eczema ☐ (39)
earache ☐ (40)
tonsillitis ☐ (41)
hepatitis ☐ (42)
rheumatic fever ☐ (43)
excess bleeding ☐ (44)
drug allergy ☐ (45)
specify: _____
_____ (46-47)

HOSPITAL ADMISSION

Current Medication . . . Drug and Dose *(please give details)*

INVESTIGATIONS

Blood Pressure ..... ☐☐☐ / ☐☐☐ (24-29)

Radiography if necessary

OPT ..... ☐ (52)

transpharyngeal ..... ☐ (53)

OM ..... ☐ (54)

periapicals ..... ☐ (55)

plain tomography ..... ☐ (56)

arthrography ..... ☐ (57)

arthroscopy ..... ☐ (58)

CT scan ..... ☐ (59)

Haematology prior to starting drug therapy

Hb ..... ☐ (60)

FBC ..... ☐ (61)

ESR ..... ☐ (62)

RhF ..... ☐ (63)

U and E's ..... ☐ (64)

LFTS ..... ☐ (65)

RESULTS

Summarise Abnormal investigations

DIAGNOSIS

	Right	Left	
facial arthromyalgia	☐	☐	(25-26)

Other: _____ ☐

TREATMENT PLAN

Admit to trial ..... yes$_1$ no$_2$ (51)

Random allocation to groups ...

Physical therapy only _____ **Bite splint** _____ ☐

Medical therapy only _____ **Fluoxetine or Placebo** ___ ☐

Physical and Medical therapy combined __ **Bite Splint + Fluoxetine** ☐

_____

_____

_____

TREATMENT FLOW CHART

WEEK	Appt. number	Drug (60)	Drug & Splint (30)	Splint (30)	Appt. number
Assessment	1	<---------- Blood	Assess and allocate Test ---------->	---------->	1
0	2	• Check blood results • Start 20mg drug	• Check blood results • Start 20 mg drug • Impressions • Inter-occlusal records	• Impressions • Inter-occlusal records	2
1					
2			• Splint fitted	• Splint fitted	3
3					
4	3	• Review medication	• Review medication • Splint review	• Splint review	4
5					
6					
7					
8	4	• Double medication	• Splint review • Double medication	• Splint review	5
9					
10					
11					
12	5	Repeat questionnaire	break code &modify	treatment if necessary	6
24	6	Repeat	questionnaires	(follow up)	7
36	7	Repeat	questionnaires	(follow up)	8

Appendix 9 – Follow-up forms

- **Pain assessment**
- **Clinical examination**
- **Splint and / or medical analysis**
- **Medication record**
- **Medication adverse events**

Completion during – 3 month treatment phase

1 month (4 weeks)
2 months (8 weeks)
3 months (12 weeks)

- 6 month follow-up phase

6 months
9 months

FOLLOW UP

DATE: ☐☐☐☐☐☐ day month year

Date of last appointment: ..... ☐☐☐☐☐☐ (24-29) day month year

Interval: ..... ☐☐ (30-31) ..... days$_1$ weeks$_2$ months$_3$ (32)

CURRENT PROBLEMS:

PAIN/DISCOMFORT: None; Mild; Moderate; Severe
SOCIAL/FAMILIAL: None; Mild; Moderate; Severe
EMOTIONAL: None; Mild; Moderate; Severe

INTERFERENCE WITH LIFE: Y / N

OTHER CURRENT SYMPTOMS: NONE; Headache, Migraine, Tinnitus; Neck Pain; Back Pain; Irritable Bowel; Pelvic Pain; Dysfunctional Uterine Bleeding; Pruritus; M.E.; Other:

DESCRIPTION OF PAIN

Character

discomfort ..... ☐ (24)
dull ache ..... ☐ (25)
burning ..... ☐ (26)
sharp ..... ☐ (27)
stabbing ..... ☐ (28)
throbbing ..... ☐ (29)

Frequency: ..... never$_1$ occasionally$_2$ often$_3$ always$_4$ (30)

Severity

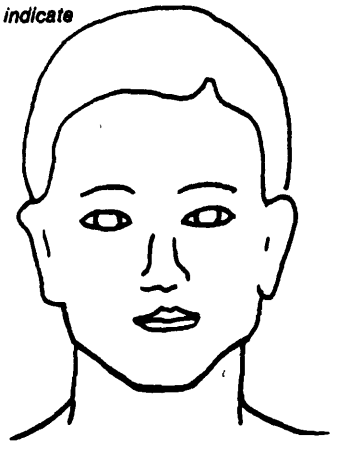
WORSE; IN PAIN; IMPROVED; PAIN FREE.

1 2 3 4 5

Site and radiation

left ..... ☐ (34)
right ..... ☐ (35)
midline ..... ☐ (36)
bilateral ..... ☐ (37)
Other: _____
_____ ☐☐ (38-39)

Please indicate



TMJ ..... ☐ (40)
face ..... ☐ (41)
scalp ..... ☐ (42)
ears ..... ☐ (43)
teeth ..... ☐ (44)
jaws and alveolus ..... ☐ (45)
palate ..... ☐ (46)
gingiva ..... ☐ (47)
tongue ..... ☐ (48)
lips ..... ☐ (49)
Other: _____
_____ ☐☐ (50-51)

EXAMINATION: T.M.J.: OPENING MM: NOISE: RT.; LT.; NIL TENDER: RT.; LT.; NIL

SPLINT ANALYSIS

SPLINT

Lost..... ☐

Broken..... ☐

At home..... ☐

Comfortable to wear..... ☐

Uncomfortable to wear..... ☐

Compliance with wearing splint..... Yes No
Stability of occlusion in relation to splint..... Good
Moderate
Poor

Adverse clinical signs of wearing splint:-

Poor oral hygiene
Gross plaque/calculus deposits ☐

Gingival.....Inflammation ☐

Swelling ☐

Bleeding ☐

Ulceration ☐

Action taken;- Splint adjustment/Oral hygiene instruction/Hygienest appt.

Splint adjustment:- Significant/Moderate/Non

Splint therapy to:- Continue/Discontinue

Next appointment:

DRUG ANALYSIS

Compliance with taking medication (as stated by patient) Yes No

Adverse effects (if yes please specify on chart) Yes No

Drug therapy to :- Continue/Discontinue

Dosage:

Next appointment:

MEDICATION

BASELINE

Other analgesics:

Name..... Quantity

Name..... Quantity

Name..... Quantity

TREATMENT PHASE

1st MONTH

Treatment drug

Quantity

Other analgesics:

Name..... Quantity

Name..... Quantity

Name..... Quantity

2nd MONTH

Treatment drug

Quantity

Other analgesics:

Name.....

Quantity

Name.....

Quantity

Name.....

Quantity

3rd MONTH

Treatment drug

Quantity

Other analgesics:

Name.....

Quantity

Name.....

Quantity

Name.....

Quantity

ADVERSE EVENTS

Rash	_____
Nausea	_____
Vomiting	_____
Diarrhoea	_____
Anorexia	_____
Headache	_____
Nervousness	_____
Insomnia	_____
Anxiety	_____
Tremor	_____
Dry mouth	_____
Dizziness	_____
Hypomania	_____
Drowsiness	_____
Convuisions	_____
Fever	_____
Sexual dysfunction	_____
Sweating	_____
Other	_____
If Yes, specify	_____
	_____

Appendix 10 – Construction and adjustment of full coverage occlusal bite guard

EASTMAN DENTAL HOSPITAL

FULL OCCLUSAL COVERAGE BITE GUARD – Construction and fitting.

This appliance provides a reversible form of therapy in which there should be no permanent occlusal changes. All the teeth in the maxillary arch are covered with heat cured acrylic and provide a hard, flat surface to engage all opposing teeth without dictating a mandibular position on closure.
On occasions mandibular appliance may be preferred firstly in patients with significant horizontal overlap of anterior in a severe class II or class III incisor relationship, or secondly where tooth loss has occurred in the mandibular arch and the appliance provides temporary replacement for the tooth in the mandibular arch and then desired occlusal requirements.

The aim is for opposing teeth to achieve stable, simultaneous contact with the appliance on mandibular closure. A gradual anterior rise is incorporated sufficiently steep to separate posterior teeth during excursive jaw movements to avoid non working side interferences and protecting posterior teeth from adverse occlusal damage.

Construction

A set of impressions are taken with an interocclusal wax record. The study casts poured in stone are mounted in a semi adjustable articulator to achieve intercuspal position. The occlusal splint is waxed incorporating a shallow incline anteriorly and thinning to approximately 1mm thickness over the occlusal surface of distal molars. The acrylic fits over the incisal edges of the maxillary anterior teeth by 1mm to ensure upper anterior teeth are not protruded labially. No additional clasps are required as natural indents on teeth provide the necessary retention. Further retention may be improved by also extending the acrylic over the buccal surface of short posterior teeth.
The appliance is then invested and processed in heat-cured acrylic resin to provide a hard, durable, flat surface. It is then returned to the articulator for further adjustment before polishing.

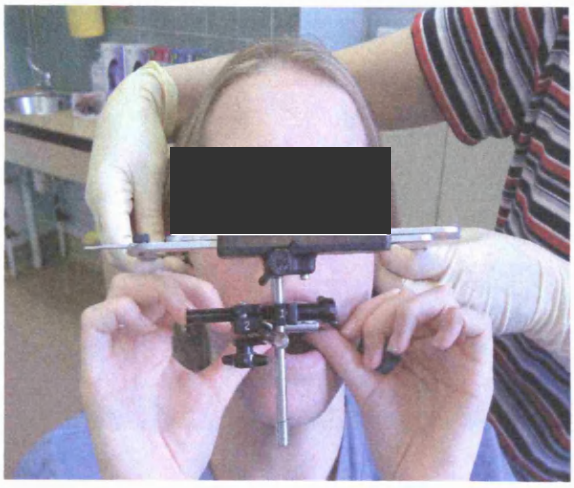
Adjustment

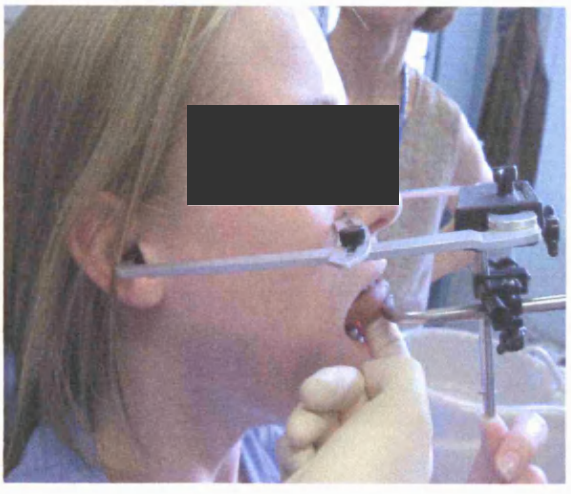
Once seated, the splint will require adjustment to achieve the correct occlusal relationship. Splint adjustments in the retruded axis position or as close to this position as possible are made first. Each posterior tooth should have a minimum of one contact with the appliance but indentations should not be created at the site of occlusal contact. Adjustments are then made for excursive movements with the aim of providing a shallow anterior guidance just sufficient to separate posterior teeth on lateral excursive movement of the mandible.
The patient may report the appliance to feel too tight at the initial appointment but encourage the patient to persevere with the tightness as the appliance will become looser within a short time of wear.

The patient should be reviewed after a fortnight for further adjustment and then at monthly intervals up to three months for minor alterations to the appliance and to assess progress of signs and symptoms.

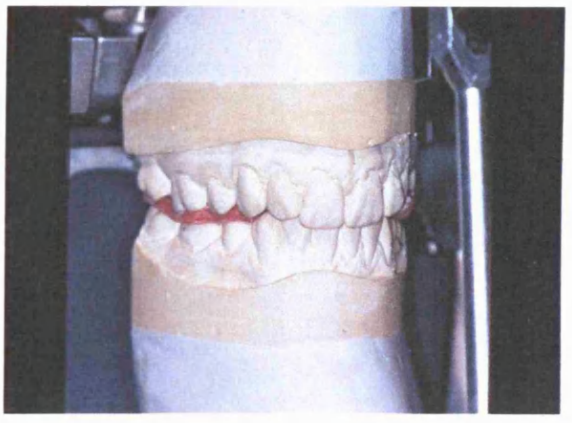
Rachel Leeson

Face bow recording for occlusal appliance construction






Wax bite and articulated models

Occlusal appliance adjustment